VIRxSYS CORPORATION

INVESTIGATIONAL NEW DRUG PROTOCOL

VRX496

PROTOCOL NUMBER VRX496-01-01

FINAL

A Phase 1 Open-Label Clinical Trial of the Safety and Tolerability of Single Escalating Doses of Autologous T Cells Transduced with VRX496 in HIV Positive Patient-Subjects

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Date Prepared: September 5, 2001

375463_10

Protocol Number: VRX496-01-01

Protocol Title: **A Phase 1 Open-Label Clinical Trial of The Safety and Tolerability of Single Escalating Doses of Autologous T Cells Transduced with VRX496 in HIV Positive Patient-subjects**

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RESTRICTED DISTRIBUTION OF PROTOCOLS

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PROTOCOL SYNOPSIS

Study Drug:	Autologous T Cells Transduced with VRX496
Protocol Number:	VRX496-01-01
Protocol Title:	A Phase 1 Open-Label Clinical Trial of the Safety and Tolerability of Single Escalating Doses of Autologous T Cells Transduced with VRX496 in HIV Positive Patient-subjects
Study Phase:	1
Study Design:	A single center, open-label, dose escalation study
Sample Size:	N = up to 24 evaluable patient-subjects
Study Population:	Male and female HIV positive patient-subjects, 18 to 60 years of age who have discontinued, or who are failing a treatment regimen of HAART.
Treatment Groups:	Individual cohorts of 3 patient-subjects or up to 6 patient-subjects will be dosed with autologous T Cells transduced with VRX496 at one of the following dose levels: 1.0×10^9; 3.0×10^9; 1.0×10^{10}; and 3.0×10^{10} transduced T cells. Dosing will begin in the initial 3 patient-subjects at the 1.0×10^9 dose level. After safety has been adequately demonstrated at the lower dose level, subsequent cohorts of 3 patient-subjects will be dosed with the next higher dose level.
Treatment Duration:	Autologous T Cells transduced with VRX496 will be infused intravenously over approximately 30 minutes. The dose volume administered will be approximately 10 to 200 mL, depending on dose.
Evaluation Schedule:	Patient-subjects will be evaluated during pre-treatment screening, at apheresis, during the infusion of Autologous T Cells transduced with VRX496, through 6 hours post infusion, at 24, 48, 72 hours, 7 days, 14 days, 28 days, 3, 6 months and yearly for the life of the patient-subject.
Objectives:	The primary objective is to assess the safety and tolerability of Autologous T Cells transduced with VRX496 in HIV positive patient-subjects. The secondary objectives are:

	• To determine the number of VRX496 modified T-lymphocytes in the blood • To determine the levels of wt-HIV and VRX496 in the plasma.
Safety Criteria:	Adverse experiences through 28 days post-dosing, Chemistry, Hematology, Urinalysis, precipitous and sustained decrease in CD4 T-cell counts, precipitous and sustained increase in wt-HIV viral load, sustained VSV-G RNA detection in plasma followed by biological detection of a VSV-G containing replication competent retrovirus (RCR).
# of VRX496 modified cells:	The number of VRX496 containing cells in the blood at 72 hours, 7, 28 days, 3, 6 months and yearly for life post dosing.
Secondary Criteria:	Changes in the anti-HIV immune response, CD4 T-cell counts, differential viral load, VSV-G antibody responses, TCR Vβ diversity analysis.

DEFINITIONS AND ASSAY SYNOPSIS

Precipitous effect:	An effect that is immediately and temporally associated with infusion of the VRX496 T cell product.
Sustained effect:	A sustained effect is an effect that is persistent over 7 days during the study with samples analyzed every other day.
Differential viral load:	TaqMan RT-PCR assay that determines the copy number of wt-HIV and VRX496 in the plasma. An adverse wt-HIV viral load would be a precipitous and sustained greater than 0.5 log increase in wt-HIV viral load from established baseline levels.
CD4 T cell count:	FACS analysis of the number of CD4 T cells in the blood. An adverse event would be a precipitous and sustained 50% reduction in CD4 T cell count from established baseline levels.
Anti-HIV immune response:	Enzyme-linked-immunospot (ELISPOT) analysis for an anti-HIV specific CD8+ cellular immune response.
Anti-HIV & anti-Tetanus Toxoid immune response:	CD4+ specific cell proliferative assay targeted to HIV or Tetanus Toxoid antigen.
TCR Vβ diversity analysis:	RT-PCR assay to detect the diversity of the TCR Vβ repertoire. Assay performed on the apheresed product, the VRX496 modified T cell infused product, and from the blood of the patient-subject 28 days post dosing.
# of VRX496 modified cells:	TaqMan DNA PCR assay detecting the number of vector containing cells in the blood.
VSV-G antibody responses:	Antibody responses to the product vector as measured by an immuno-based assay.
VSV-G RNA in plasma:	VSV-G RNA in the plasma will be monitored by TaqMan RT-PCR. A sustained detection of VSV-G RNA would require biological Replication Competent Retrovirus (RCR) testing to determine if RCR is present.
Biological RCR test:	Apheresed cells will be tested for RCR by co-culture of 10^8 cells on an indicator cell line that is not permissive to wt-HIV replication. After 6 passages, the supernatant will be tested for HIV gag RNA by TaqMan RT-PCR. An adverse event would be a positive HIV gag TaqMan RT-PCR signal after amplification on the indicator cell line.

1.0 INTRODUCTION

HIV infects 36.1 million people worldwide (UNAIDS 2000). In the United States (U.S.), it is estimated that over 425,000 people are infected with HIV, and over 45,000 new cases are reported each year (CDC, 2000). AIDS is defined by the CDC as occurring in all HIV-infected individuals that have a CD4+ T cell count of less than 200/mm^3. This definition also includes 26 conditions affecting people with HIV, including *P. carinii* pneumonia, HIV wasting syndrome, CMV disease, tuberculosis, Kaposi's sarcoma, disseminated *M. avium*, chronic Herpes simplex, recurrent bacterial pneumonia, HIV-associated dementia, and toxoplasmosis (Bartlett, 2001). The majority of these conditions are opportunistic infections that are often severe and sometimes fatal, because the ravaged immune system can no longer fight off infection. The mortality due to HIV/AIDS is estimated to be approximately 3 million deaths annually worldwide, and 15,000 in the U.S. (UNAIDS, 2000;CDC, 2000).

HIV belongs to a family of retroviruses known as lentiviruses. These RNA viruses are characterized by possession of the enzyme reverse transcriptase that transcribes the viral RNA into provirus DNA that is integrated into the host cell genome.

There are currently 16 Food and Drug Administration (FDA) approved drug products for the treatment of HIV infection (CRIA, 2001). The current standard of treatment for HIV/AIDS is the highly active antiretroviral therapy (HAART). This therapy typically consists of a triple "cocktail" of a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) and a protease inhibitor (PI). Although these cocktails have been successful in reducing viral loads and restoring immune function, they do not represent a cure, and there are concerns regarding adverse effects associated with long-term usage of HAART. Specifically, a variety of metabolic disorders including HIV-associated lipodystrophy, central adiposity, dyslipidaemia, hyperlipidaemia, hyperglycemia and insulin resistance have been reported as resulting from HAART (Vigouroux, 1999; Behrens, 2000). These reactions,

combined with complex and cumbersome dosing regimes, can have an adverse impact on patient-subject adherence to therapy (Lucas, 1999; Max, 2000).

A number of different genetic antiviral strategies have been utilized to combat HIV-1, including antisense RNA, trans-dominant proteins, ribozymes, RNA decoys, and single chain antibodies (Dropulic and Jeang, 1994; Veres et al, 1998). Antisense RNA gene transfer offers a significant advantage over several other genetic antiviral approaches since it is not a protein and thus not immunogenic.

HIV-based lentiviral vectors are being proposed as the delivery system for novel antisense genetic therapy. All lentiviruses encode the gag, pol, and envelope (env) proteins, and it is the env protein that mediates the infection of susceptible cells by HIV (Buchschacher and Wong-Staal 2000). Since lentivirus vectors integrate into the host cell DNA, they provide useful tools for permanently introducing exogenous genes into cells.

VIRxSYS Corporation (VIRxSYS) in Gaithersburg, Maryland is developing a proprietary compound vector VRX496.

VRX496 is an HIV-based lentiviral vector harboring an anti-HIV antisense sequence targeted to the HIV envelope (env) coding sequence. VRX496 has been developed as a proprietary gene transfer product for the treatment of human immunodeficiency virus (HIV) infection, via autologous T cell transduction ex vivo and subsequent reintroduction to the patient-subject.

HIV-based vectors provide numerous advantages over current HIV combination therapies. The HIV vector targets only those cells already infected with Wild type-HIV (Wt-HIV) and expression of an antiviral gene is dependent entirely on this wt-virus. Secondly, HIV vectors are predicted to be safe since no new genetic sequences are introduced into the patient-subject. And the HIV sequences that are used are from pNL4-3, which is one of the most common molecular clones of HIV-1.

1.1 Preclinical Pharmacology And Safety Data

Preliminary in vitro testing was performed in human immune cells (from blood drawn from human donors) using anti-HIV vectors VRX496 and VRX496 analogs. The cells were ex vivo modified with anti-HIV vectors and then infected with HIV. Results from this testing repeatedly showed a reduction in HIV viral replication by as much as 99% and that the loss of CD4 T cells was significantly prevented. Preliminary results from experiments in SCID-hu mice (mice with transplanted human lymphocytes) indicate that the human cells transduced with VRX496 and implanted into the SCID mice do not elicit any overt adverse effects. Maintaining CD4 cells is the key factor for restoring the immune system in HIV subjects. These data suggest that HIV-based vectors such as VRX496 have the potential to reduce viral loads in HIV-infected individuals. This could prolong the delay to the onset to AIDS while promoting CD4+ T-cell survival, and provide the immune system with a better chance to control the infection.

In addition, two pivotal non-clinical safety assessment studies are ongoing with normal human T cells transduced with VRX496. The biodistribution and safety of human T-cells transduced with VRX496 are being examined in SCID/SCID mice at dose levels representing approximately 1 and 75 times the proposed clinical starting dose (10^9 transduced T cells/patient-subject). These dose multiples are based upon a 20 g mouse and a 75 kg human. Preliminary results from these studies show no toxicity through animal sacrifice at 30 days.

For additional information, please refer to the Investigator's Brochure for Autologous T-cells Transduced with VRX496.

2.0 STUDY PURPOSE AND OBJECTIVES

2.1 Purpose

The purpose of this study is to determine the safety and tolerability of single doses of VRX496 modified T-cells in HIV positive patient-subjects at 4 different dose levels.

2.2 Study Objectives

Primary Objective:

- To determine the safety and tolerability of intravenous administration of autologous VRX496 modified T-cells in HIV positive patient-subjects.

Secondary Objectives:

- To determine the number of VRX496 modified T cells in the blood.
- To determine the levels of wt-HIV and VRX496 in the plasma.
- To determine changes in the anti-HIV immune response
- To determine if there are changes to the TCR Vβ repertoire
- To monitor VSV-G antibody levels that may be due to the vector

3.0 TRIAL DESIGN

3.1 Description of Trial Design

Protocol VRX496-01-01 is a single-center, open-label, single-dose, dose-escalation study of the safety and tolerability of intravenous administration of VRX496 modified T-cells in HIV positive patient-subjects.

Up to 24 HIV positive patient-subjects meeting the study inclusion criteria will be enrolled into the study with up to 6 patient-subjects treated at each of the following 4 dose levels:

Dose Level 1 – approximately 1.0×10^9 VRX496 modified T-cells,

Dose Level 2 – approximately 3.0×10^9 VRX496 modified T-cells,

Dose Level 3 – approximately 1.0×10^{10} VRX496 modified T-cells, and

Dose Level 4 – approximately 3.0×10^{10} VRX496 modified T-cells.

The initial patient-subjects enrolled will be assigned to treatment with the first dose level (1.0×10^9 VRX496 modified T-cells). After the 28-day patient-subject clinical and laboratory safety has been established at the current dose level, dosing will proceed to the next higher dose level according to the dose escalation scheme outlined in Section 3.1.1.

The maximum tolerated dose (MTD) will be defined as the dose level immediately below the level at which greater than or equal to two patient-subjects develop DLT.

3.1.1 Dose Escalation Scheme

Following dosing with VRX496 modified T-cells, patient-subjects will be evaluated for dose limiting toxicity through 28-days post-dosing. Severity of observed toxicities will be graded using the AIDS Clinical Trials Group (ACTG) toxicity criteria provided in Appendix A. Dose limiting laboratory toxicity (DLT) will be defined as any of the following :

- hematologic toxicity greater than or equal to ACTG Grade 3 (*Note: If a patient-subject demonstrates Grade 3 or greater Laboratory Toxicity the investigator will immediately repeat the test to confirm the result. For the purpose of dose escalation, if the repeat test does not confirm the toxicity, the patient-subject will not be considered to have experienced a dose limiting laboratory toxicity*), or
- non – hematologic toxicity of ACTG Grade 4, or
- sustained (i.e., persistent over 7 days in duration) increase from baseline in wt-HIV viral load of a magnitude of 0.5 log or greater, or
- sustained (i.e., persistent over 7 days in duration) decrease from baseline in CD4+ T-cell count of 50% or greater, or
- sustained (i.e., persistent over 7 days in duration) presence of VSV-G RNA in the plasma followed by a positive biological RCR test.

Dose escalation will proceed as follows:

- Three patient-subjects will be enrolled at each dose level and followed for dose limiting toxicity through 28-days post dosing. Dose escalation will proceed upon approval of the Data Safety Monitoring Board (DSMB). *Note: for Dose Level 1, the initial patient-subject treated must*

be followed through 28-days prior to the treatment of the remaining patient-subjects in the Dose Level. For Dose Levels 2, 3 and 4 the initial patient-subjects may be treated and followed concurrently.

- If no dose limiting toxicity is observed, dosing may proceed to the next higher dose level.
- If one of the initial three patient-subjects demonstrates a dose limiting toxicity, an additional three patient-subjects will be studied at the current dose level. If no additional dose limiting toxicity is observed dosing may proceed to the next higher dose level.
- The Data and Safety Monitoring Board will review data from each dose level and approve escalation to the next higher dose level.
- Patient-subject treatment and dose escalation will cease if two (2) patient-subjects at a dose level exhibit a dose limiting toxicity.
- Patient-subject treatment and dose escalation will cease if a single (1) patient-subject demonstrates the presence of a Replication Competent Retrovirus (RCR), as defined by the biological RCR test.

A diagram of the dose escalation scheme is provided as Appendix D.

3.2 Study Endpoints

3.2.1 Primary Safety Endpoints

The primary safety endpoints are:

- The incidence of adverse events at each dose level studied from dosing through 28-days post-dosing,
- The incidence of serious adverse events and dose limiting toxicity at each dose level studied from dosing through 28-days post-dosing, and
- The changes in clinical chemistry, hematology and urinalysis test results at each time point from dosing through 28 days post-dosing.

be followed through 28-days prior to the treatment of the remaining patient-subjects in the Dose Level. For Dose Levels 2, 3 and 4 the initial patient-subjects may be treated and followed concurrently.

- If no dose limiting toxicity is observed, dosing may proceed to the next higher dose level.
- If one of the initial three patient-subjects demonstrates a dose limiting toxicity, an additional three patient-subjects will be studied at the current dose level. If no additional dose limiting toxicity is observed dosing may proceed to the next higher dose level.
- The Data and Safety Monitoring Board will review data from each dose level and approve escalation to the next higher dose level.
- Patient-subject treatment and dose escalation will cease if two (2) patient-subjects at a dose level exhibit a dose limiting toxicity.
- Patient-subject treatment and dose escalation will cease if a single (1) patient-subject demonstrates the presence of a Replication Competent Retrovirus (RCR), as defined by the biological RCR test.

A diagram of the dose escalation scheme is provided as Appendix D.

3.2 Study Endpoints

3.2.1 Primary Safety Endpoints

The primary safety endpoints are:

- The incidence of adverse events at each dose level studied from dosing through 28-days post-dosing,
- The incidence of serious adverse events and dose limiting toxicity at each dose level studied from dosing through 28-days post-dosing, and
- The changes in clinical chemistry, hematology and urinalysis test results at each time point from dosing through 28 days post-dosing.

- The changes in viral load and CD4 T cell count from dosing through 28-days post-dosing.

3.2.2 Secondary Endpoints

The secondary endpoints of this study will focus on long term safety, changes in indices of HIV infection and cell survival of VRX496 containing T-lymphocytes as follows:

- The incidence of serious adverse events through 6 months post-dosing,
- The change in differential viral load from pre-dose levels through 6-months post dosing, and
- The change in CD4+ T-cell counts from pre-dose levels through 6-months post dosing.
- Immune function (by HIV virus specific CD4 cell proliferative responses, Tetanus Toxoid specific CD4 proliferative responses, ELISPOT measurement of IFN-gamma producing CD8 T cells, & TCR Vβ diversity analysis)
- VSV-G antibody responses to the product vector

3.3 Evaluation Criteria

The evaluation criteria used to assess the safety and tolerability of VRX496 modified T-cells are standard safety assessments used in clinical trials and meet the safety objectives of this study.

3.3.1 Safety Criteria

Safety of VRX496 modified T-cells will be assessed by changes from Baseline through Day - 28 in physical examination, ECG and chest x-ray findings and the following laboratory evaluations:

- Clinical Chemistry parameters defined in Section 5.4
- Hematology parameters defined in Section 5.4
- Urinalysis parameters defined in Section 5.4
- Virological, cellular and immune parameters defined in Section 5.4

Serum β HCG pregnancy test will be drawn for all women of child bearing potential at screening and within 24-hours prior to dosing.

Adverse events that occur after the administration of VRX496-modified T-Cells (Day – 0) through Day 28 will be recorded (see Section 5.6). The severity and relationship to treatment for all adverse events will be assessed by the Investigator using the definitions provided in Section 5.6.

3.3.2 Secondary Evaluation Criteria

The secondary evaluation criteria of patient-subjects treated with VRX496-modified T-Cells include:

- Indices of HIV infection, CD4+ T-cell counts, differential viral load levels, VSV-G antibody and immune function (by CD4+ proliferation assay, ELISPOT and TCR Vβ diversity measurements) will be assessed through to 6-months post-dosing.

3.3.3 Survival of VRX496 modified T-cells

The survival of VRX496-modified T-cells will be determined by measuring the average vector copy number in the blood by TaqMan PCR through 6 months post dosing and then yearly for the life of the patient.

3.4 Methods to Minimize Bias

3.4.1 Blinding

This is not a blinded study. All patient-subjects treated under this protocol will be treated with active drug product using an escalating dose study design. The criteria for the assessment of safety are well defined and subject to minimal bias in reporting. The efficacy criteria utilized are laboratory derived and not subject to bias.

3.4.2 Randomization

The dose-escalation nature of this study does not make randomizing patient-subjects to a particular treatment group feasible. Consecutive patient-subjects who are consented and pass all screening evaluations will be assigned to the next available treatment number.

The investigator will be required to maintain a patient-subject screening and treatment log and to document the reason(s) consented patient-subjects were not determined to be eligible for the study.

3.5 Study Treatments

3.5.1 Description of Study Treatments

Dose Level 1 (approximately 1.0×10^9 VRX496 transduced T-cells)

Dose Level 2 (approximately 3.0×10^9 VRX496 transduced T-cells),

Dose Level 3 (approximately 1.0×10^{10} VRX496 transduced T-cells), and

Dose Level 4 (approximately 3.0×10^{10} VRX496 transduced T-cells).

3.5.2 Rationale for Dosage Regimen and Choice of Control Groups

The initial dose level of VRX496 modified T cells (approximately 1.0×10^9) was chosen because:

- The dose is 75 times lower than the maximum dose used in nonclinical toxicology studies and shown to be safe, and
- Is the lowest dose level that will allow for detection of VRX496 modified T-cells in the blood.

Subsequent dose levels will increase by approximately 0.5 log increments to permit a determination of dose-response relationship for the safety and secondary evaluation parameters obtained.

There will not be a control group used for this study.

3.5.3 Treatment Compliance

Qualified research personnel will administer VRX496-modified T-cells to each patient-subject as a single intravenous infusion in a controlled research facility. Research personnel will record the date and time the infusion is started and stopped. There are no anticipated issues with compliance with study medication administration.

3.5.4 Prior and Concomitant Therapy

Patient-subjects are prohibited from taking the following medications during the course of the study (i.e., from screening through 6-month post treatment follow-up):

- Immunomodulating agents (IL-2, IFN-Gamma, Granulocyte colony stimulating factors, Megace)
- Any experimental therapy for HIV or other indications
- Corticosteroids
- Hydroxyurea
- Additional antiretroviral medication regimes. If a patient-subject is currently receiving an antiretroviral regimen, that regimen must be continued for the 6-month duration of the trial.

3.6 Study Compliance

This trial will be conducted in compliance with the study protocol, ICH and Good Clinical Practice (GCP) guidelines, and all applicable regulatory requirements.

4.0 STUDY POPULATION

4.1 Inclusion Criteria

- Male and female patient-subjects 18 – 60 years of age who are HIV positive.
- Karnofsky Performance Score of 80 or higher (see appendix E).
- Patient-subjects who have received HAART therapy for at least 6 months and have either discontinued, or are failing treatment.

- Patient-subjects with a documented CD4 T-cell count greater than 200/mm^3 but less than 600/mm^3 within 30 days prior to screening.
- Patient-subjects with a documented viral load of greater than 500 copies within 30 days prior to screening.
- Patient-subjects who understand and agree to be compliant with the requirements for the 6-month duration of the study and the necessity for annual follow up for life. At the time of death an autopsy will be performed.
- Patient-subjects who have provided written informed consent after the nature of the study has been explained.

4.2 Exclusion Criteria

- Patient-subjects who have not been treated with a previous regimen of HAART.
- Patient-subjects who are pregnant or breast-feeding.
- Patient-subjects who have a recent (within 1 year) history of drug abuse and or a positive urine drug/alcohol test at time of screening.
- Patient-subjects who are currently taking corticosteroids or who have taken corticosteroids within the past 30 days.
- Patient-subjects who have received hydroxyurea within the prior 30 days. Note: Patient-subjects currently taking hydroxyurea may be enrolled if the use of hydroxyurea is discontinued at least 30 days prior to apheresis.
- Patient-subjects taking immunomodulating agents (e.g., IL-2, IFN-Gamma, Granulocyte Colony stimulating factors, Megace)
- Previous treatment with HIV experimental vaccine(s).
- Patient-subjects taking antibiotics within one week prior to receiving study medication.

- Patient-subjects currently in the treatment or recovery phase of an acute infection (e.g., sinusitis).
- Patient-subjects who have received acute treatment of a serious Opportunistic Infection (OI) within the past 30 days.
- Patient-subjects who have undergone leukopheresis or lymphopheresis within 90 days of entry into the study.
- Patient-subjects who have active CNS disease or seizures within 1 year.
- Patient-subjects who have active MAI Infection or CMV Disease.
- Patient-subjects who have a history of cerebral toxoplasmosis or cryptococcal meningitis.
- Patient-subjects with a history of cancer.
- Patient-subjects with a history of Class III or IV congestive heart failure
- Patient-subjects with the following laboratory abnormalities: Hemoglobin of less than 10 for males and less than 9.5 for females; absolute neutrophil count less than 1000/μL; platelet count of less than 100,000/mm^3; serum creatinine greater than 1.5 mg/dL; AST or ALT greater than 2.5 times the upper limit of normal; total serum bilirubin greater than 1.5 times the upper limit of normal; amylase & lipase outside normal range; and proteinuria of 2+ or greater.
- Patient-subjects who have participated in a prior gene therapy trial.
- Patient-subjects who have previously received treatment under this protocol or are currently being treated under another research protocol.
- Patient-subjects with a significant medical history who in the opinion of the investigator would be placed at risk by being enrolled in this study.

4.3 Discontinuation Criteria

A patient-subject may be withdrawn from the study prior to drug treatment at the investigator's discretion if any of the following occurs:

- Clinically significant deterioration that impairs the global status/condition of the patient-subject.
- Investigator decides discontinuation is in the best interest of the patient-subject.
- Patient-subject requests withdrawal from the study.
- Patient-subject is enrolled and subsequently becomes ineligible for study participation due to a change in patient-subject status that meets exclusionary criteria. (e.g., addition of prohibited medication, pregnancy).

Patient-subjects withdrawing from the study for any of the above reasons will be considered terminated and will be replaced. The reason for study termination will be documented in the patient-subject's medical record and recorded on the appropriate page of the case report form.

All patient-subjects receiving VRX496-modified T-cells must be followed for the entire 6 months. In the event a patient-subject fails to complete the follow up requirements through Day 28, the patient-subject will be replaced to permit the determination of the maximum tolerated dose. If a patient-subject fails to keep follow-up appointments, the site must document all attempts to contact the patient-subject. Minimum follow-up contact requirements will include at least 3 telephone contacts (on different days and at different times of the day) and a certified letter.

VIRxSYS may at their discretion terminate the study as a whole if conditions warrant that this action be taken. If the study is stopped, treated patient-subjects must be followed for the entire 6-month follow up period. The study site investigator maintains responsibility for orderly discontinuation of the study at his/her study site.

5.0 STUDY PROCEDURES

5.1 Pre-Screening

The investigator must keep a list of all patient-subjects who have been evaluated for their eligibility to enter the study. This evaluation may be based on a telephone interview or review of medical records prior to the patient-subject's first clinic visit and prior to any protocol specific procedures being performed. The investigator and staff should evaluate potential patient-subjects for compliance with follow up requirements (as outlined in Section 5.4).

During a routine monitoring visit the monitor may request to review this pre-screening list to evaluate site metrics. Patient-subjects who pass the initial pre-screen (i.e., meet all inclusion criteria and do not have any exclusion criteria) will be further evaluated for inclusion in the study during the screening phase (Section 5.4.1). A Pre-Screening worksheet will be provided to all sites and will include the following information:

- Date that patient-subject was screened,
- Patient-subject initials,
- Patient-subject's Date of Birth
- Eligible for inclusion (yes or no),
- If eligible, treatment ID assigned, date consent obtained and person obtaining informed consent, and
- If not eligible, the reason the patient-subject was excluded.

5.2 Assignment to Treatment

Each patient-subject consented for admission into the study will be assigned a sequential screening number by the investigator beginning with S001 and screening procedures will be performed as described in section 5.4.1. Consented patient-subjects who pass all screening evaluations will be assigned the next available treatment number which corresponds to one of the 4 dose levels as follows:

Dose Level 1 (approximately 1.0×10^9 VRX496 transduced T-cells)

Dose Level 2 (approximately 3.0×10^9 VRX496 transduced T-cells),

Dose Level 3 (approximately 1.0×10^{10} VRX496 transduced T-cells), and

Dose Level 4 (approximately 3.0×10^{10} VRX496 transduced T-cells).

5.3 Clinical and Laboratory Procedures

5.3.1 Inclusion/Exclusion Criteria

Criteria for inclusion and exclusion, specified in Sections 4.1 and 4.2, will be outlined in a checklist in the case report form (CRF). These criteria determine patient-subject eligibility for selection. All patient-subject criteria must be evaluated for the presence of all inclusion criteria and the absence of all exclusion criteria before enrollment in this study.

5.3.2 Medical History

Background information will be recorded once for each patient-subject during screening for this study. This includes age, gender, race and medical history including an HIV history, concomitant diseases, conditions and medications.

Patient-subjects will also be requested to provide current contact information to facilitate patient-subject contact. Minimal information required will include address and telephone number and name of an alternate contact person if the patient-subject cannot be reached. The Investigator will maintain patient-subject contact information in a confidential manner and the information will only be used to contact the patient-subject regarding this study in the event the need arises.

5.3.3 Physical Examination

All patient-subjects will have a complete physical examination including vital signs at screening, pre dosing, 24 hours, 48 hours, 72 hours, 7, 14, and 28 days post dosing. Height will be recorded once at screening and weight will be recorded at pre-dosing and at 28 days. Any change from screening physical examination that is clinically significant and noted during follow-up will be recorded in the patient-subject's medical record and on the CRF..

5.3.4 Electrocardiogram

All patient-subjects will have an a twelve lead electrocardiogram (ECG) performed at screening, pre-dosing, 24 hours and 28 days post dosing.

5.3.5 Chest X-Ray

Chest X-ray will be performed within 30 days prior to dosing and at 28 days post dosing.

5.3.6 Apheresis

Apheresis will be performed twice for all eligible and consented patient-subjects. After eligibility is confirmed an apheresis procedure will be scheduled and repeated at the 6 month follow up visit. Apheresis may be requested earlier if VSV-G RNA is detected in the plasma in a sustained manner.

The apheresis procedure will be performed in the blood bank at the University of Pennsylvania Medical Center in accordance with institutional standard operating procedures and supervised by trained study personnel. The procedure will take approximately 2-3 hours to complete.

Patient-subjects will be have vital signs (blood pressure, heart rate, respiratory rate) measured and recorded every 15 minutes following completion of the apheresis procedure for one hour. If the patient-subject's vital signs are not stable after one hour, vital signs will continue to be monitored every 15 minutes until the patient-subject is stable.

The first apheresis product will be packaged, labeled, stored and transferred to the Clinical Cell and Vaccine Production Facility at the University of Pennsylvania in accordance with institutional standard operating procedures for transduction with the VRX496 cell product. The VRX496-modified T-cells is the drug product reintroduced into the patient-subject. The second apheresis product will not be returned to the patient-subject.

5.3.7 Concomitant Medications

All prescription and nonprescription medication (excluding vitamins and nutritional supplements) taken by the patient-subject from 30 days prior to screening and up to and including the 28 days following dosing will be recorded in the medical record and on the CRF. Any additions, deletions, or changes in the dose of these medications must be recorded. Therapy prohibited by the study protocol is outlined in Section 3.5.4.

5.3.8 Laboratory Procedures

The following parameters* will be measured using the clinic's local laboratory facilities. The following parameters+ will be measured at VIRxSYS facilities. All other parameters will be measured at the University of Pennsylvania.

*Hematology: Hemoglobin, hematocrit, platelet count, RBC and WBC with differential at screening, prior to dosing, 24 hours, 72 hours, Days 7, 14 and 28 after dosing.

*PT and PTT: at screening, prior to dosing, 24 hours, and 28 days after dosing.

*Serum Chemistry: Sodium, Potassium, Chloride, Bicarbonate, CO2, Urea Nitrogen, Creatinine, Total Protein, Albumin, Calcium, Phosphorous, Alkaline Phosphatase, Total Bilirubin, Cholesterol, Triglyceride, amylase, lipase, ALT, AST, GGT, and LDH at screening, prior to dosing, 24 hours, 72 hours, Days 7, 14 and 28 after dosing.

*Urinalysis: pH, Specific gravity, glucose, protein, ketones and microscopic (WBC, RBC, epithelial cells, casts, and crystals) at screening, prior to dosing, 24 hours, 72 hours and Days 7, 14 and 28.

*Serum Pregnancy Test: for women of childbearing potential at screening and within 24 hours prior to dosing

*CD4 count: performed at screening, prior to dosing, 72 hours, Days 7 and 28 and 3 and 6 months after dosing.

+Differential Viral Load: performed at screening, prior to dosing, 72 hours, 7, 28 days, 3 and 6 months after dosing.

Anti-HIV immune response: Anti-HIV ELISPOT and CD4 T cell proliferation assay is performed prior to dosing, 72 hours, 7, 28 days, 3 and 6 months after dosing.

Anti-Tetanus Toxoid (TT) response: Anti-TT cell proliferation assay is performed prior to dosing, 72 hours, 7, 28 days, 3 and 6 months after dosing.

+Number of VRX496 modified cells: performed immediately prior to dosing, immediately after dosing, 72 hours, 7, 28 days, 3, 6 months and yearly after dosing.

+VSV-G RNA in plasma: performed immediately prior to dosing, 72 hours, 7, 28 days, 3, 6 months and yearly after dosing.

+Biological RCR test: performed at the 6 month apheresis or earlier if sustained VSV-G RNA is detected in the plasma.

+VSV-G antibody responses: Immuno-based assay to detect for vector specific antibody responses performed prior to dosing, at 72 hours, 7, 28 days, 3, 6 months and yearly after dosing.

TCR Vβ diversity analysis: RT-PCR assay to detect for the diversity of the T cell receptor repertoire. Performed on the first apheresed product, the VRX496 modified T cell infused product and at 28 days post dosing.

5.3.9 Safety Procedures

All adverse experiences will be recorded from the time of treatment to the end of the study regardless of causal relationship. Clinically significant changes from screening in physical examination are considered to be adverse experiences and will be recorded in the patient-subject's medical record. Reporting of adverse experiences is discussed in Section 5.6.

5.3.10 Toxicity Management

Dose limiting toxicities will be managed as deemed medically appropriate. Dose limiting laboratory toxicities observed will be followed as described below:

- If a patient-subject demonstrates Grade 3 or greater Laboratory Toxicity the investigator will immediately repeat the test to confirm the result. Laboratory toxicities should be followed until resolution or until no further improvement is anticipated by the Investigator.

- If a patient-subject experiences an immediate precipitous and sustained increase from baseline in viral load of greater than 0.5 logs, then the viral load will then be followed every other day for 7 days to determine if the increase is a sustained result.

- If a patient-subject experiences a immediate precipitous decrease from baseline in CD4+ T-cell count of 50% or greater. CD4+ T-cell count will then be followed every other day for 7 days to determine if the decrease is a sustained result.

- If a patient-subject experiences detection of VSV-G RNA, VSV-G antibody response will be followed every other day for 7 days to determine if the detection is a sustained result.

5.3.11 Screen Failures

Patient-subjects will be considered to be a screen failure if any of the following occur:

– Patient-subject consented and is determined to be not eligible based upon results of screening procedures.

– Patient-subject consented and determined eligible for the study but develops an exclusionary condition or withdraws consent prior to dosing.

5.4 Schedule of Procedures

The evaluation schedule for the study is provided in Appendix C.

5.4.1 Screening

An investigator must explain the nature of the study protocol and risks associated with the protocol in detail to the patient-subject. The patient-subject must sign and date his/her written informed consent prior to participation in the study. The date of the Informed Consent will be recorded in the patient-subject's medical record and on the case report form. Screening procedures will include:

- A review of Inclusion/Exclusion Criteria
- Medical History
- Physical Examination including vital signs, height and weight
- Review of concomitant medications
- Hematology (WBC with differential, RBC, Hct, Hgb and platelets)
- PT and PTT
- Chemistry (Sodium, Potassium, Chloride, Bicarbonate, CO2, Urea Nitrogen, Creatinine, Glucose, Total Protein, Albumin, Calcium, Phosphorous, Alkaline Phosphatase. Total Bilirubin, Cholesterol, Triglyceride, lipase, amylase, ALT, AST, GGT, GGT, LDH)
- Urinalysis
- CD4 level (if patient-subject has a documented CD4 level within 30 days of screening this will be accepted)
- Viral Load (if patient-subject has a documented viral load within 30 days of screening this will be accepted) and Differential Viral Load (to establish comparability between standard and TaqMan RT-PCR viral load assays
- 12 lead Electrocardiogram (ECG)
- Chest X-ray (within 30 days prior to dosing)
- Serum β HCG pregnancy (women of childbearing potential).

5.4.2 Apheresis

After all required evaluations are completed and eligibility is confirmed by the principal investigator consented patient-subjects will undergo apheresis.

Patient-subjects will also have an apheresis procedure performed at the six-month follow up timepoint.

5.4.3 Prior to Dosing

Within twenty-four (24) hours prior to patient-subject receiving Autologous CD4 T Cells Transduced with VRX496 the following must be performed:

- Physical Exam (including vital signs)
- Chemistry
- Hematology
- PT and PTT
- Urinalysis
- Serum Pregnancy Test (for women of childbearing potential)
- 12- lead ECG
- CD4+ T-cell counts
- Differential Viral Load
- Anti-HIV immune response – ELISPOT
- Anti-HIV & Anti-Tetanus Toxoid CD4 proliferation assay
- # of VRX496 modified Cells
- VSV-G RNA in plasma
- VSV-G antibody response
- Review of Concomitant Medications
- Adverse Events

5.4.4 VRX496 Administration

- On the day of patient-subject dosing, VRX496-modified T cells will be transported from the Clinical Cell Production Facility to the study site at University of Pennsylvania Hospital.
- VRX496-modified T cells will be thawed in a 37°C water bath at patient-subject bedside immediately after transport. Cells will be infused within 5-30 minutes after thaw.
- The VRX496-modified T cells (approximately 1.0×10^8 cells/mL) drug product will be immediately infused intravenously at a rate of

approximately 10 mL/minute through a 18G latex free Y-type blood set with 3 way stop-cock. Dosing will take place by gravity infusion. If the infusion rate by gravity is too slow, the VRX496-modified T cells drug product may be drawn into a 50mL syringe via the stopcock and manually infused at the required rate. The infusion volumes for each dose level are as follows:

Dose Level 1 (approximately $1.0x10^9$ cells) – approximately 10 mL

Dose Level 2 (approximately $3.0x10^9$ cells) – approximately 30 mL

Dose Level 3 (approximately $1.0x10^{10}$cells) – approximately 100 mL

Dose Level 4 (approximately $3.0x10^{10}$ cells) – approximately 300 mL

- Within 15 minutes (± 5 minutes) following completion of dosing with VRX496 modified T-cells a blood sample will be obtained for VRX496containing T-lymphocytes.
- Blood pressure, heart rate, respiratory rate and pulse oximetry will be obtained and recorded immediately prior to dosing and every 15 minutes for 2 hours following the start of infusion. If vital signs are not stable 2 hours following the start of infusion, measurements will continue to be obtained every 15 minutes until the patient-subject's vital signs are stable
- Patient-subjects will remain in the inpatient Clinical Research Center (CRC) for 2 hours post infusion for observation. If no symptoms occur and patient-subject's vital signs are stable, patient-subject will be discharged.
- Patient-subjects will be instructed to return to the CRC in 24 hours for blood tests and follow up.

5.4.5 Twenty-Four (24) hours after Dosing

- Physical Exam (including vital signs)
- Chemistry
- Hematology
- PT and PTT
- Urinalysis
- 12 lead ECG

- Review of Concomitant Medications
- Adverse Events

5.4.6 Forty-eight (48) hours after Dosing

- Physical Exam (including vital signs)
- Review of Concomitant Medications
- Adverse Events

5.4.7 Seventy-two (72) hours after Dosing

- Physical Exam (including vital signs)
- Chemistry
- Hematology
- Urinalysis
- CD4+ T-cell counts
- Differential Viral Load
- Anti-HIV immune response – ELISPOT
- Anti-HIV & Anti-Tetanus Toxoid CD4 proliferation assay
- # of VRX496 modified Cells
- VSV-G RNA in plasma
- VSV-G antibody response
- Review of Concomitant Medications
- Adverse Events

5.4.8 Seven (7) Days post dosing

- Physical Exam
- Chemistry
- Hematology
- Urinalysis
- CD4+ T-cell counts
- Differential Viral Load
- Anti-HIV immune response – ELISPOT
- Anti-HIV & Anti-Tetanus Toxoid CD4 proliferation assay
- # of VRX496 modified Cells
- VSV-G RNA in plasma

- VSV-G antibody response
- Review of Concomitant Medications
- Adverse Events

5.4.9 Fourteen (14) Days post dosing

- Physical Exam (including vital signs)
- Review of Concomitant Medications
- Adverse Events

5.4.10 Twenty-eight (28) Days post dosing

- Physical Exam (including vital signs)
- 12 lead ECG
- CD4+ T-cell counts
- Differential Viral Load
- Anti-HIV immune response – ELISPOT
- Anti-HIV & Anti-Tetanus Toxoid CD4 proliferation assay
- # of VRX496 modified Cells
- VSV-G RNA in plasma
- VSV-G antibody response
- TCR Vβ diversity analysis
- Chest X-ray
- Hematology
- PT/PTT
- Chemistry
- Urinalysis
- Review of Concomitant Medications
- Adverse Events

5.4.11 Three (3)-months post dosing

- CD4+ T-cell counts
- Differential Viral Load
- Anti-HIV immune response – ELISPOT
- Anti-HIV & Anti-Tetanus Toxoid CD4 proliferation assay
- # of VRX496 modified Cells

- VSV-G RNA in plasma
- VSV-G antibody response

5.4.12 Six (6)-months post dosing

- CD4+ T-cell counts
- Differential Viral Load
- Anti-HIV immune response – ELISPOT
- Anti-HIV & Anti-Tetanus Toxoid CD4 proliferation assay
- # of VRX496 modified Cells
- VSV-G RNA in plasma
- VSV-G antibody response
- Biological RCR test
- Second research Apheresis
- Medical History

5.4.13 One year post dosing and annually for life

- CD4+ T-cell counts
- Differential Viral Load
- Anti-HIV immune response – ELISPOT
- Anti-HIV & Anti-Tetanus Toxoid CD4 proliferation assay
- # of VRX496 modified Cells
- VSV-G RNA in plasma
- VSV-G antibody response
- Medical History

Note: If all post treatment assays are negative during the first year, the yearly samples should be archived. Samples should be archived with appropriate safeguards to ensure long-term storage (e.g., a monitored freezer alarm storage system) and an efficient system for the prompt linkage and retrieval of the stored samples with the medical records of the patient-subject and the production lot records.

If any post-treatment samples are positive, further analysis and more extensive patient-subject follow-up should be undertaken. At the time of collection of yearly patient-subject specimens, a brief clinical history should be obtained. This history should be targeted towards determination of clinical outcomes suggestive of retroviral disease.

5.5 Premature Discontinuation of Study Patient-subjects

A patient-subject is considered to be a premature discontinuation if their participation is terminated prior to completion of all required visits/evaluations specified in Sections 5.4.1 through 5.4.13 of the protocol.

A patient-subject may be discontinued for the following reasons:

- Non-Compliance with treatment regimen or follow up requirements
- Lost To Follow-Up
- Patient-subject Request for Voluntary Withdrawal
- Adverse Event
- Investigator Decision

If a patient-subject is prematurely discontinued prior to Day-28 from the study, all Day-28 procedures will be performed. If a patient-subject is prematurely discontinued following the Twenty-eight (28) Day evaluation, all 6-month procedures will be performed.

5.6 Recording of Adverse Events

Each patient-subject will be observed and queried in a nonspecific fashion by the investigator or his/her designee at each visit during the study for any new or continuing AEs since the previous visit. Any AE reported by the patient-subject or noted by the investigator or his/her designee will be recorded on the Adverse Experience Case Report Form. The following information will be recorded for each reported AE: description of the event, time of onset, time of resolution, severity, drug relationship determination, outcome, and management of the AE.

5.6.1 Potential Adverse Events

This is the first protocol using VRX496 in humans and the safety profile in humans is unknown. Adverse clinical events reported in clinical trials with infusion of gene-modified T-cells have been chills, fever, headache, nausea, rigors, bronchospasm, myalgias and blurred vision.

Patient-subjects may also experience a metallic taste in the mouth, hypertension, bradycardia, allergic reaction, and seizures due to the DMSO component of the final formulation. Nausea, vomiting, decreased hemoglobin and hematocrit, increased AST and ALT, hypersensitivity reaction anaphylaxis and thrombophlebitis may be observed from the Dextran-40 component of the formulation.

The apheresis procedure may be associated with the following adverse events: nausea, vomiting, seizures, blood loss, infection, skin rash, flushing, hives, numbness and tingling, bruising at the site of venous access, lightheadedness, and lower extremity edema.

5.6.2 Definitions

Adverse events (AEs) are defined as Treatment Emergent Signs and Symptoms (TESS). These are events that are not seen at screening, or, if present at screening have worsened in severity.

Study drug relationship for each adverse experience should be determined by the investigator using the following definitions:

NOT RELATED:
This category applies to those adverse experiences, which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).

UNLIKELY: (Must have 2)
In general, this category can be considered applicable to those adverse experiences, which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug. An adverse experience may be considered unlikely to be related if or when:

VIRxSYS CORPORATION

INVESTIGATIONAL NEW DRUG PROTOCOL

VRX496

PROTOCOL NUMBER VRX496-01-01

FINAL

A Phase 1 Open-Label Clinical Trial of the Safety and Tolerability of Single Escalating Doses of Autologous T Cells Transduced with VRX496 in HIV Positive Patient-Subjects

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Date Prepared: September 5, 2001

375463_10

Protocol Number: VRX496-01-01

Protocol Title: **A Phase 1 Open-Label Clinical Trial of The Safety and Tolerability of Single Escalating Doses of Autologous T Cells Transduced with VRX496 in HIV Positive Patient-subjects**

University of Pennsylvania approvals:

Rob Roy MacGregor, MD
Principal Investigator — Date

Carl H June, MD
Sub-Investigator and Sponsor, Cell Manufacturing — Date

VIRxSYS approvals:

Boro Dropulic, PhD
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VIRxSYS' Contract Research Organization, TheraSolutions, approvals:

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Manager, Clinical Operations — Date

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Thomas Genna, RPh
Director, Clinical Research — Date

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President, TheraSolutions — Date

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Investigational New Drug Protocol

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LIST OF APPENDICES

RESTRICTED DISTRIBUTION OF PROTOCOLS

This protocol contains information that is proprietary to VIRxSYS Corporation (VIRxSYS). The information contained herein is provided for the purpose of conducting a clinical trial for VIRxSYS.

The contents of this protocol may be disclosed to study personnel under your supervision and to your Institutional Review Board(s). The contents of this protocol may not be disclosed to any other parties (unless such disclosure is required by government regulations or laws) without prior written approval from VIRxSYS.

PROTOCOL SYNOPSIS

Study Drug:	Autologous T Cells Transduced with VRX496
Protocol Number:	VRX496-01-01
Protocol Title:	A Phase 1 Open-Label Clinical Trial of the Safety and Tolerability of Single Escalating Doses of Autologous T Cells Transduced with VRX496 in HIV Positive Patient-subjects
Study Phase:	1
Study Design:	A single center, open-label, dose escalation study
Sample Size:	N = up to 24 evaluable patient-subjects
Study Population:	Male and female HIV positive patient-subjects, 18 to 60 years of age who have discontinued, or who are failing a treatment regimen of HAART.
Treatment Groups:	Individual cohorts of 3 patient-subjects or up to 6 patient-subjects will be dosed with autologous T Cells transduced with VRX496 at one of the following dose levels: 1.0×10^9; 3.0×10^9; 1.0×10^{10}; and 3.0×10^{10} transduced T cells. Dosing will begin in the initial 3 patient-subjects at the 1.0×10^9 dose level. After safety has been adequately demonstrated at the lower dose level, subsequent cohorts of 3 patient-subjects will be dosed with the next higher dose level.
Treatment Duration:	Autologous T Cells transduced with VRX496 will be infused intravenously over approximately 30 minutes. The dose volume administered will be approximately 10 to 200 mL, depending on dose.
Evaluation Schedule:	Patient-subjects will be evaluated during pre-treatment screening, at apheresis, during the infusion of Autologous T Cells transduced with VRX496, through 6 hours post infusion, at 24, 48, 72 hours, 7 days, 14 days, 28 days, 3, 6 months and yearly for the life of the patient-subject.
Objectives:	The primary objective is to assess the safety and tolerability of Autologous T Cells transduced with VRX496 in HIV positive patient-subjects. The secondary objectives are:

	• To determine the number of VRX496 modified T-lymphocytes in the blood • To determine the levels of wt-HIV and VRX496 in the plasma.
Safety Criteria:	Adverse experiences through 28 days post-dosing, Chemistry, Hematology, Urinalysis, precipitous and sustained decrease in CD4 T-cell counts, precipitous and sustained increase in wt-HIV viral load, sustained VSV-G RNA detection in plasma followed by biological detection of a VSV-G containing replication competent retrovirus (RCR).
# of VRX496 modified cells:	The number of VRX496 containing cells in the blood at 72 hours, 7, 28 days, 3, 6 months and yearly for life post dosing.
Secondary Criteria:	Changes in the anti-HIV immune response, CD4 T-cell counts, differential viral load, VSV-G antibody responses, TCR Vβ diversity analysis.

DEFINITIONS AND ASSAY SYNOPSIS

Precipitous effect:	An effect that is immediately and temporally associated with infusion of the VRX496 T cell product.
Sustained effect:	A sustained effect is an effect that is persistent over 7 days during the study with samples analyzed every other day.
Differential viral load:	TaqMan RT-PCR assay that determines the copy number of wt-HIV and VRX496 in the plasma. An adverse wt-HIV viral load would be a precipitous and sustained greater than 0.5 log increase in wt-HIV viral load from established baseline levels.
CD4 T cell count:	FACS analysis of the number of CD4 T cells in the blood. An adverse event would be a precipitous and sustained 50% reduction in CD4 T cell count from established baseline levels.
Anti-HIV immune response:	Enzyme-linked-immunospot (ELISPOT) analysis for an anti-HIV specific CD8+ cellular immune response.
Anti-HIV & anti-Tetanus Toxoid immune response:	CD4+ specific cell proliferative assay targeted to HIV or Tetanus Toxoid antigen.
TCR Vβ diversity analysis:	RT-PCR assay to detect the diversity of the TCR Vβ repertoire. Assay performed on the apheresed product, the VRX496 modified T cell infused product, and from the blood of the patient-subject 28 days post dosing.
# of VRX496 modified cells:	TaqMan DNA PCR assay detecting the number of vector containing cells in the blood.
VSV-G antibody responses:	Antibody responses to the product vector as measured by an immuno-based assay.
VSV-G RNA in plasma:	VSV-G RNA in the plasma will be monitored by TaqMan RT-PCR. A sustained detection of VSV-G RNA would require biological Replication Competent Retrovirus (RCR) testing to determine if RCR is present.
Biological RCR test:	Apheresed cells will be tested for RCR by co-culture of 10^8 cells on an indicator cell line that is not permissive to wt-HIV replication. After 6 passages, the supernatant will be tested for HIV gag RNA by TaqMan RT-PCR. An adverse event would be a positive HIV gag TaqMan RT-PCR signal after amplification on the indicator cell line.

1.0 INTRODUCTION

HIV infects 36.1 million people worldwide (UNAIDS 2000). In the United States (U.S.), it is estimated that over 425,000 people are infected with HIV, and over 45,000 new cases are reported each year (CDC, 2000). AIDS is defined by the CDC as occurring in all HIV-infected individuals that have a CD4+ T cell count of less than 200/mm^3. This definition also includes 26 conditions affecting people with HIV, including *P. carinii* pneumonia, HIV wasting syndrome, CMV disease, tuberculosis, Kaposi's sarcoma, disseminated *M. avium*, chronic Herpes simplex, recurrent bacterial pneumonia, HIV-associated dementia, and toxoplasmosis (Bartlett, 2001). The majority of these conditions are opportunistic infections that are often severe and sometimes fatal, because the ravaged immune system can no longer fight off infection. The mortality due to HIV/AIDS is estimated to be approximately 3 million deaths annually worldwide, and 15,000 in the U.S. (UNAIDS, 2000;CDC, 2000).

HIV belongs to a family of retroviruses known as lentiviruses. These RNA viruses are characterized by possession of the enzyme reverse transcriptase that transcribes the viral RNA into provirus DNA that is integrated into the host cell genome.

There are currently 16 Food and Drug Administration (FDA) approved drug products for the treatment of HIV infection (CRIA, 2001). The current standard of treatment for HIV/AIDS is the highly active antiretroviral therapy (HAART). This therapy typically consists of a triple "cocktail" of a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) and a protease inhibitor (PI). Although these cocktails have been successful in reducing viral loads and restoring immune function, they do not represent a cure, and there are concerns regarding adverse effects associated with long-term usage of HAART. Specifically, a variety of metabolic disorders including HIV-associated lipodystrophy, central adiposity, dyslipidaemia, hyperlipidaemia, hyperglycemia and insulin resistance have been reported as resulting from HAART (Vigouroux, 1999; Behrens, 2000). These reactions,

combined with complex and cumbersome dosing regimes, can have an adverse impact on patient-subject adherence to therapy (Lucas, 1999; Max, 2000).

A number of different genetic antiviral strategies have been utilized to combat HIV-1, including antisense RNA, trans-dominant proteins, ribozymes, RNA decoys, and single chain antibodies (Dropulic and Jeang, 1994; Veres et al, 1998). Antisense RNA gene transfer offers a significant advantage over several other genetic antiviral approaches since it is not a protein and thus not immunogenic.

HIV-based lentiviral vectors are being proposed as the delivery system for novel antisense genetic therapy. All lentiviruses encode the gag, pol, and envelope (env) proteins, and it is the env protein that mediates the infection of susceptible cells by HIV (Buchschacher and Wong-Staal 2000). Since lentivirus vectors integrate into the host cell DNA, they provide useful tools for permanently introducing exogenous genes into cells.

VIRxSYS Corporation (VIRxSYS) in Gaithersburg, Maryland is developing a proprietary compound vector VRX496.

VRX496 is an HIV-based lentiviral vector harboring an anti-HIV antisense sequence targeted to the HIV envelope (env) coding sequence. VRX496 has been developed as a proprietary gene transfer product for the treatment of human immunodeficiency virus (HIV) infection, via autologous T cell transduction ex vivo and subsequent reintroduction to the patient-subject.

HIV-based vectors provide numerous advantages over current HIV combination therapies. The HIV vector targets only those cells already infected with Wild type-HIV (Wt-HIV) and expression of an antiviral gene is dependent entirely on this wt-virus. Secondly, HIV vectors are predicted to be safe since no new genetic sequences are introduced into the patient-subject. And the HIV sequences that are used are from pNL4-3, which is one of the most common molecular clones of HIV-1.

1.1 Preclinical Pharmacology And Safety Data

Preliminary in vitro testing was performed in human immune cells (from blood drawn from human donors) using anti-HIV vectors VRX496 and VRX496 analogs. The cells were ex vivo modified with anti-HIV vectors and then infected with HIV. Results from this testing repeatedly showed a reduction in HIV viral replication by as much as 99% and that the loss of CD4 T cells was significantly prevented. Preliminary results from experiments in SCID-hu mice (mice with transplanted human lymphocytes) indicate that the human cells transduced with VRX496 and implanted into the SCID mice do not elicit any overt adverse effects. Maintaining CD4 cells is the key factor for restoring the immune system in HIV subjects. These data suggest that HIV-based vectors such as VRX496 have the potential to reduce viral loads in HIV-infected individuals. This could prolong the delay to the onset to AIDS while promoting CD4+ T-cell survival, and provide the immune system with a better chance to control the infection.

In addition, two pivotal non-clinical safety assessment studies are ongoing with normal human T cells transduced with VRX496. The biodistribution and safety of human T-cells transduced with VRX496 are being examined in SCID/SCID mice at dose levels representing approximately 1 and 75 times the proposed clinical starting dose (10^9 transduced T cells/patient-subject). These dose multiples are based upon a 20 g mouse and a 75 kg human. Preliminary results from these studies show no toxicity through animal sacrifice at 30 days.

For additional information, please refer to the Investigator's Brochure for Autologous T-cells Transduced with VRX496.

2.0 STUDY PURPOSE AND OBJECTIVES

2.1 Purpose

The purpose of this study is to determine the safety and tolerability of single doses of VRX496 modified T-cells in HIV positive patient-subjects at 4 different dose levels.

2.2 Study Objectives

Primary Objective:

- To determine the safety and tolerability of intravenous administration of autologous VRX496 modified T-cells in HIV positive patient-subjects.

Secondary Objectives:

- To determine the number of VRX496 modified T cells in the blood.
- To determine the levels of wt-HIV and VRX496 in the plasma.
- To determine changes in the anti-HIV immune response
- To determine if there are changes to the TCR Vβ repertoire
- To monitor VSV-G antibody levels that may be due to the vector

3.0 TRIAL DESIGN

3.1 Description of Trial Design

Protocol VRX496-01-01 is a single-center, open-label, single-dose, dose-escalation study of the safety and tolerability of intravenous administration of VRX496 modified T-cells in HIV positive patient-subjects.

Up to 24 HIV positive patient-subjects meeting the study inclusion criteria will be enrolled into the study with up to 6 patient-subjects treated at each of the following 4 dose levels:

Dose Level 1 – approximately 1.0×10^9 VRX496 modified T-cells,

Dose Level 2 – approximately 3.0×10^9 VRX496 modified T-cells,

Dose Level 3 – approximately 1.0×10^{10} VRX496 modified T-cells, and

Dose Level 4 – approximately 3.0×10^{10} VRX496 modified T-cells.

The initial patient-subjects enrolled will be assigned to treatment with the first dose level (1.0×10^9 VRX496 modified T-cells). After the 28-day patient-subject clinical and laboratory safety has been established at the current dose level, dosing will proceed to the next higher dose level according to the dose escalation scheme outlined in Section 3.1.1.

The maximum tolerated dose (MTD) will be defined as the dose level immediately below the level at which greater than or equal to two patient-subjects develop DLT.

3.1.1 Dose Escalation Scheme

Following dosing with VRX496 modified T-cells, patient-subjects will be evaluated for dose limiting toxicity through 28-days post-dosing. Severity of observed toxicities will be graded using the AIDS Clinical Trials Group (ACTG) toxicity criteria provided in Appendix A. Dose limiting laboratory toxicity (DLT) will be defined as any of the following :

- hematologic toxicity greater than or equal to ACTG Grade 3 (*Note: If a patient-subject demonstrates Grade 3 or greater Laboratory Toxicity the investigator will immediately repeat the test to confirm the result. For the purpose of dose escalation, if the repeat test does not confirm the toxicity, the patient-subject will not be considered to have experienced a dose limiting laboratory toxicity*), or
- non – hematologic toxicity of ACTG Grade 4, or
- sustained (i.e., persistent over 7 days in duration) increase from baseline in wt-HIV viral load of a magnitude of 0.5 log or greater, or
- sustained (i.e., persistent over 7 days in duration) decrease from baseline in CD4+ T-cell count of 50% or greater, or
- sustained (i.e., persistent over 7 days in duration) presence of VSV-G RNA in the plasma followed by a positive biological RCR test.

Dose escalation will proceed as follows:

- Three patient-subjects will be enrolled at each dose level and followed for dose limiting toxicity through 28-days post dosing. Dose escalation will proceed upon approval of the Data Safety Monitoring Board (DSMB). *Note: for Dose Level 1, the initial patient-subject treated must*

be followed through 28-days prior to the treatment of the remaining patient-subjects in the Dose Level. For Dose Levels 2, 3 and 4 the initial patient-subjects may be treated and followed concurrently.

- If no dose limiting toxicity is observed, dosing may proceed to the next higher dose level.
- If one of the initial three patient-subjects demonstrates a dose limiting toxicity, an additional three patient-subjects will be studied at the current dose level. If no additional dose limiting toxicity is observed dosing may proceed to the next higher dose level.
- The Data and Safety Monitoring Board will review data from each dose level and approve escalation to the next higher dose level.
- Patient-subject treatment and dose escalation will cease if two (2) patient-subjects at a dose level exhibit a dose limiting toxicity.
- Patient-subject treatment and dose escalation will cease if a single (1) patient-subject demonstrates the presence of a Replication Competent Retrovirus (RCR), as defined by the biological RCR test.

A diagram of the dose escalation scheme is provided as Appendix D.

3.2 Study Endpoints

3.2.1 Primary Safety Endpoints

The primary safety endpoints are:

- The incidence of adverse events at each dose level studied from dosing through 28-days post-dosing,
- The incidence of serious adverse events and dose limiting toxicity at each dose level studied from dosing through 28-days post-dosing, and
- The changes in clinical chemistry, hematology and urinalysis test results at each time point from dosing through 28 days post-dosing.

be followed through 28-days prior to the treatment of the remaining patient-subjects in the Dose Level. For Dose Levels 2, 3 and 4 the initial patient-subjects may be treated and followed concurrently.

- If no dose limiting toxicity is observed, dosing may proceed to the next higher dose level.
- If one of the initial three patient-subjects demonstrates a dose limiting toxicity, an additional three patient-subjects will be studied at the current dose level. If no additional dose limiting toxicity is observed dosing may proceed to the next higher dose level.
- The Data and Safety Monitoring Board will review data from each dose level and approve escalation to the next higher dose level.
- Patient-subject treatment and dose escalation will cease if two (2) patient-subjects at a dose level exhibit a dose limiting toxicity.
- Patient-subject treatment and dose escalation will cease if a single (1) patient-subject demonstrates the presence of a Replication Competent Retrovirus (RCR), as defined by the biological RCR test.

A diagram of the dose escalation scheme is provided as Appendix D.

3.2 Study Endpoints

3.2.1 Primary Safety Endpoints

The primary safety endpoints are:

- The incidence of adverse events at each dose level studied from dosing through 28-days post-dosing,
- The incidence of serious adverse events and dose limiting toxicity at each dose level studied from dosing through 28-days post-dosing, and
- The changes in clinical chemistry, hematology and urinalysis test results at each time point from dosing through 28 days post-dosing.

- The changes in viral load and CD4 T cell count from dosing through 28-days post-dosing.

3.2.2 Secondary Endpoints

The secondary endpoints of this study will focus on long term safety, changes in indices of HIV infection and cell survival of VRX496 containing T-lymphocytes as follows:

- The incidence of serious adverse events through 6 months post-dosing,
- The change in differential viral load from pre-dose levels through 6-months post dosing, and
- The change in CD4+ T-cell counts from pre-dose levels through 6-months post dosing.
- Immune function (by HIV virus specific CD4 cell proliferative responses, Tetanus Toxoid specific CD4 proliferative responses, ELISPOT measurement of IFN-gamma producing CD8 T cells, & TCR Vβ diversity analysis)
- VSV-G antibody responses to the product vector

3.3 Evaluation Criteria

The evaluation criteria used to assess the safety and tolerability of VRX496 modified T-cells are standard safety assessments used in clinical trials and meet the safety objectives of this study.

3.3.1 Safety Criteria

Safety of VRX496 modified T-cells will be assessed by changes from Baseline through Day - 28 in physical examination, ECG and chest x-ray findings and the following laboratory evaluations:

- Clinical Chemistry parameters defined in Section 5.4
- Hematology parameters defined in Section 5.4
- Urinalysis parameters defined in Section 5.4
- Virological, cellular and immune parameters defined in Section 5.4

Serum β HCG pregnancy test will be drawn for all women of child bearing potential at screening and within 24-hours prior to dosing.

Adverse events that occur after the administration of VRX496-modified T-Cells (Day – 0) through Day 28 will be recorded (see Section 5.6). The severity and relationship to treatment for all adverse events will be assessed by the Investigator using the definitions provided in Section 5.6.

3.3.2 Secondary Evaluation Criteria

The secondary evaluation criteria of patient-subjects treated with VRX496-modified T-Cells include:

- Indices of HIV infection, CD4+ T-cell counts, differential viral load levels, VSV-G antibody and immune function (by CD4+ proliferation assay, ELISPOT and TCR Vβ diversity measurements) will be assessed through to 6-months post-dosing.

3.3.3 Survival of VRX496 modified T-cells

The survival of VRX496-modified T-cells will be determined by measuring the average vector copy number in the blood by TaqMan PCR through 6 months post dosing and then yearly for the life of the patient.

3.4 Methods to Minimize Bias

3.4.1 Blinding

This is not a blinded study. All patient-subjects treated under this protocol will be treated with active drug product using an escalating dose study design. The criteria for the assessment of safety are well defined and subject to minimal bias in reporting. The efficacy criteria utilized are laboratory derived and not subject to bias.

3.4.2 Randomization

The dose-escalation nature of this study does not make randomizing patient-subjects to a particular treatment group feasible. Consecutive patient-subjects who are consented and pass all screening evaluations will be assigned to the next available treatment number.

The investigator will be required to maintain a patient-subject screening and treatment log and to document the reason(s) consented patient-subjects were not determined to be eligible for the study.

3.5 Study Treatments

3.5.1 Description of Study Treatments

Dose Level 1 (approximately 1.0×10^9 VRX496 transduced T-cells)

Dose Level 2 (approximately 3.0×10^9 VRX496 transduced T-cells),

Dose Level 3 (approximately 1.0×10^{10} VRX496 transduced T-cells), and

Dose Level 4 (approximately 3.0×10^{10} VRX496 transduced T-cells).

3.5.2 Rationale for Dosage Regimen and Choice of Control Groups

The initial dose level of VRX496 modified T cells (approximately 1.0×10^9) was chosen because:

- The dose is 75 times lower than the maximum dose used in nonclinical toxicology studies and shown to be safe, and
- Is the lowest dose level that will allow for detection of VRX496 modified T-cells in the blood.

Subsequent dose levels will increase by approximately 0.5 log increments to permit a determination of dose-response relationship for the safety and secondary evaluation parameters obtained.

There will not be a control group used for this study.

3.5.3 Treatment Compliance

Qualified research personnel will administer VRX496-modified T-cells to each patient-subject as a single intravenous infusion in a controlled research facility. Research personnel will record the date and time the infusion is started and stopped. There are no anticipated issues with compliance with study medication administration.

3.5.4 Prior and Concomitant Therapy

Patient-subjects are prohibited from taking the following medications during the course of the study (i.e., from screening through 6-month post treatment follow-up):

- Immunomodulating agents (IL-2, IFN-Gamma, Granulocyte colony stimulating factors, Megace)
- Any experimental therapy for HIV or other indications
- Corticosteroids
- Hydroxyurea
- Additional antiretroviral medication regimes. If a patient-subject is currently receiving an antiretroviral regimen, that regimen must be continued for the 6-month duration of the trial.

3.6 Study Compliance

This trial will be conducted in compliance with the study protocol, ICH and Good Clinical Practice (GCP) guidelines, and all applicable regulatory requirements.

4.0 STUDY POPULATION

4.1 Inclusion Criteria

- Male and female patient-subjects 18 – 60 years of age who are HIV positive.
- Karnofsky Performance Score of 80 or higher (see appendix E).
- Patient-subjects who have received HAART therapy for at least 6 months and have either discontinued, or are failing treatment.

- Patient-subjects with a documented CD4 T-cell count greater than 200/mm^3 but less than 600/mm^3 within 30 days prior to screening.
- Patient-subjects with a documented viral load of greater than 500 copies within 30 days prior to screening.
- Patient-subjects who understand and agree to be compliant with the requirements for the 6-month duration of the study and the necessity for annual follow up for life. At the time of death an autopsy will be performed.
- Patient-subjects who have provided written informed consent after the nature of the study has been explained.

4.2 Exclusion Criteria

- Patient-subjects who have not been treated with a previous regimen of HAART.
- Patient-subjects who are pregnant or breast-feeding.
- Patient-subjects who have a recent (within 1 year) history of drug abuse and or a positive urine drug/alcohol test at time of screening.
- Patient-subjects who are currently taking corticosteroids or who have taken corticosteroids within the past 30 days.
- Patient-subjects who have received hydroxyurea within the prior 30 days. Note: Patient-subjects currently taking hydroxyurea may be enrolled if the use of hydroxyurea is discontinued at least 30 days prior to apheresis.
- Patient-subjects taking immunomodulating agents (e.g., IL-2, IFN-Gamma, Granulocyte Colony stimulating factors, Megace)
- Previous treatment with HIV experimental vaccine(s).
- Patient-subjects taking antibiotics within one week prior to receiving study medication.

- Patient-subjects currently in the treatment or recovery phase of an acute infection (e.g., sinusitis).
- Patient-subjects who have received acute treatment of a serious Opportunistic Infection (OI) within the past 30 days.
- Patient-subjects who have undergone leukopheresis or lymphopheresis within 90 days of entry into the study.
- Patient-subjects who have active CNS disease or seizures within 1 year.
- Patient-subjects who have active MAI Infection or CMV Disease.
- Patient-subjects who have a history of cerebral toxoplasmosis or cryptococcal meningitis.
- Patient-subjects with a history of cancer.
- Patient-subjects with a history of Class III or IV congestive heart failure
- Patient-subjects with the following laboratory abnormalities: Hemoglobin of less than 10 for males and less than 9.5 for females; absolute neutrophil count less than 1000/μL; platelet count of less than 100,000/mm^3; serum creatinine greater than 1.5 mg/dL; AST or ALT greater than 2.5 times the upper limit of normal; total serum bilirubin greater than 1.5 times the upper limit of normal; amylase & lipase outside normal range; and proteinuria of 2+ or greater.
- Patient-subjects who have participated in a prior gene therapy trial.
- Patient-subjects who have previously received treatment under this protocol or are currently being treated under another research protocol.
- Patient-subjects with a significant medical history who in the opinion of the investigator would be placed at risk by being enrolled in this study.

4.3 Discontinuation Criteria

A patient-subject may be withdrawn from the study prior to drug treatment at the investigator's discretion if any of the following occurs:

- Clinically significant deterioration that impairs the global status/condition of the patient-subject.
- Investigator decides discontinuation is in the best interest of the patient-subject.
- Patient-subject requests withdrawal from the study.
- Patient-subject is enrolled and subsequently becomes ineligible for study participation due to a change in patient-subject status that meets exclusionary criteria. (e.g., addition of prohibited medication, pregnancy).

Patient-subjects withdrawing from the study for any of the above reasons will be considered terminated and will be replaced. The reason for study termination will be documented in the patient-subject's medical record and recorded on the appropriate page of the case report form.

All patient-subjects receiving VRX496-modified T-cells must be followed for the entire 6 months. In the event a patient-subject fails to complete the follow up requirements through Day 28, the patient-subject will be replaced to permit the determination of the maximum tolerated dose. If a patient-subject fails to keep follow-up appointments, the site must document all attempts to contact the patient-subject. Minimum follow-up contact requirements will include at least 3 telephone contacts (on different days and at different times of the day) and a certified letter.

VIRxSYS may at their discretion terminate the study as a whole if conditions warrant that this action be taken. If the study is stopped, treated patient-subjects must be followed for the entire 6-month follow up period. The study site investigator maintains responsibility for orderly discontinuation of the study at his/her study site.

5.0 STUDY PROCEDURES

5.1 Pre-Screening

The investigator must keep a list of all patient-subjects who have been evaluated for their eligibility to enter the study. This evaluation may be based on a telephone interview or review of medical records prior to the patient-subject's first clinic visit and prior to any protocol specific procedures being performed. The investigator and staff should evaluate potential patient-subjects for compliance with follow up requirements (as outlined in Section 5.4).

During a routine monitoring visit the monitor may request to review this pre-screening list to evaluate site metrics. Patient-subjects who pass the initial pre-screen (i.e., meet all inclusion criteria and do not have any exclusion criteria) will be further evaluated for inclusion in the study during the screening phase (Section 5.4.1). A Pre-Screening worksheet will be provided to all sites and will include the following information:

- Date that patient-subject was screened,
- Patient-subject initials,
- Patient-subject's Date of Birth
- Eligible for inclusion (yes or no),
- If eligible, treatment ID assigned, date consent obtained and person obtaining informed consent, and
- If not eligible, the reason the patient-subject was excluded.

5.2 Assignment to Treatment

Each patient-subject consented for admission into the study will be assigned a sequential screening number by the investigator beginning with S001 and screening procedures will be performed as described in section 5.4.1. Consented patient-subjects who pass all screening evaluations will be assigned the next available treatment number which corresponds to one of the 4 dose levels as follows:

Dose Level 1 (approximately 1.0×10^9 VRX496 transduced T-cells)

Dose Level 2 (approximately 3.0×10^9 VRX496 transduced T-cells),

Dose Level 3 (approximately 1.0×10^{10} VRX496 transduced T-cells), and

Dose Level 4 (approximately 3.0×10^{10} VRX496 transduced T-cells).

5.3 Clinical and Laboratory Procedures

5.3.1 Inclusion/Exclusion Criteria

Criteria for inclusion and exclusion, specified in Sections 4.1 and 4.2, will be outlined in a checklist in the case report form (CRF). These criteria determine patient-subject eligibility for selection. All patient-subject criteria must be evaluated for the presence of all inclusion criteria and the absence of all exclusion criteria before enrollment in this study.

5.3.2 Medical History

Background information will be recorded once for each patient-subject during screening for this study. This includes age, gender, race and medical history including an HIV history, concomitant diseases, conditions and medications.

Patient-subjects will also be requested to provide current contact information to facilitate patient-subject contact. Minimal information required will include address and telephone number and name of an alternate contact person if the patient-subject cannot be reached. The Investigator will maintain patient-subject contact information in a confidential manner and the information will only be used to contact the patient-subject regarding this study in the event the need arises.

5.3.3 Physical Examination

All patient-subjects will have a complete physical examination including vital signs at screening, pre dosing, 24 hours, 48 hours, 72 hours, 7, 14, and 28 days post dosing. Height will be recorded once at screening and weight will be recorded at pre-dosing and at 28 days. Any change from screening physical examination that is clinically significant and noted during follow-up will be recorded in the patient-subject's medical record and on the CRF..

5.3.4 Electrocardiogram

All patient-subjects will have an a twelve lead electrocardiogram (ECG) performed at screening, pre-dosing, 24 hours and 28 days post dosing.

5.3.5 Chest X-Ray

Chest X-ray will be performed within 30 days prior to dosing and at 28 days post dosing.

5.3.6 Apheresis

Apheresis will be performed twice for all eligible and consented patient-subjects. After eligibility is confirmed an apheresis procedure will be scheduled and repeated at the 6 month follow up visit. Apheresis may be requested earlier if VSV-G RNA is detected in the plasma in a sustained manner.

The apheresis procedure will be performed in the blood bank at the University of Pennsylvania Medical Center in accordance with institutional standard operating procedures and supervised by trained study personnel. The procedure will take approximately 2-3 hours to complete.

Patient-subjects will be have vital signs (blood pressure, heart rate, respiratory rate) measured and recorded every 15 minutes following completion of the apheresis procedure for one hour. If the patient-subject's vital signs are not stable after one hour, vital signs will continue to be monitored every 15 minutes until the patient-subject is stable.

The first apheresis product will be packaged, labeled, stored and transferred to the Clinical Cell and Vaccine Production Facility at the University of Pennsylvania in accordance with institutional standard operating procedures for transduction with the VRX496 cell product. The VRX496-modified T-cells is the drug product reintroduced into the patient-subject. The second apheresis product will not be returned to the patient-subject.

5.3.7 Concomitant Medications

All prescription and nonprescription medication (excluding vitamins and nutritional supplements) taken by the patient-subject from 30 days prior to screening and up to and including the 28 days following dosing will be recorded in the medical record and on the CRF. Any additions, deletions, or changes in the dose of these medications must be recorded. Therapy prohibited by the study protocol is outlined in Section 3.5.4.

5.3.8 Laboratory Procedures

The following parameters* will be measured using the clinic's local laboratory facilities. The following parameters+ will be measured at VIRxSYS facilities. All other parameters will be measured at the University of Pennsylvania.

*Hematology: Hemoglobin, hematocrit, platelet count, RBC and WBC with differential at screening, prior to dosing, 24 hours, 72 hours, Days 7, 14 and 28 after dosing.

*PT and PTT: at screening, prior to dosing, 24 hours, and 28 days after dosing.

*Serum Chemistry: Sodium, Potassium, Chloride, Bicarbonate, CO2, Urea Nitrogen, Creatinine, Total Protein, Albumin, Calcium, Phosphorous, Alkaline Phosphatase, Total Bilirubin, Cholesterol, Triglyceride, amylase, lipase, ALT, AST, GGT, and LDH at screening, prior to dosing, 24 hours, 72 hours, Days 7, 14 and 28 after dosing.

*Urinalysis: pH, Specific gravity, glucose, protein, ketones and microscopic (WBC, RBC, epithelial cells, casts, and crystals) at screening, prior to dosing, 24 hours, 72 hours and Days 7, 14 and 28.

*Serum Pregnancy Test: for women of childbearing potential at screening and within 24 hours prior to dosing

*CD4 count: performed at screening, prior to dosing, 72 hours, Days 7 and 28 and 3 and 6 months after dosing.

+Differential Viral Load: performed at screening, prior to dosing, 72 hours, 7, 28 days, 3 and 6 months after dosing.

Anti-HIV immune response: Anti-HIV ELISPOT and CD4 T cell proliferation assay is performed prior to dosing, 72 hours, 7, 28 days, 3 and 6 months after dosing.

Anti-Tetanus Toxoid (TT) response: Anti-TT cell proliferation assay is performed prior to dosing, 72 hours, 7, 28 days, 3 and 6 months after dosing.

+Number of VRX496 modified cells: performed immediately prior to dosing, immediately after dosing, 72 hours, 7, 28 days, 3, 6 months and yearly after dosing.

+VSV-G RNA in plasma: performed immediately prior to dosing, 72 hours, 7, 28 days, 3, 6 months and yearly after dosing.

+Biological RCR test: performed at the 6 month apheresis or earlier if sustained VSV-G RNA is detected in the plasma.

+VSV-G antibody responses: Immuno-based assay to detect for vector specific antibody responses performed prior to dosing, at 72 hours, 7, 28 days, 3, 6 months and yearly after dosing.

TCR Vβ diversity analysis: RT-PCR assay to detect for the diversity of the T cell receptor repertoire. Performed on the first apheresed product, the VRX496 modified T cell infused product and at 28 days post dosing.

5.3.9 Safety Procedures

All adverse experiences will be recorded from the time of treatment to the end of the study regardless of causal relationship. Clinically significant changes from screening in physical examination are considered to be adverse experiences and will be recorded in the patient-subject's medical record. Reporting of adverse experiences is discussed in Section 5.6.

5.3.10 Toxicity Management

Dose limiting toxicities will be managed as deemed medically appropriate. Dose limiting laboratory toxicities observed will be followed as described below:

- If a patient-subject demonstrates Grade 3 or greater Laboratory Toxicity the investigator will immediately repeat the test to confirm the result. Laboratory toxicities should be followed until resolution or until no further improvement is anticipated by the Investigator.

- If a patient-subject experiences an immediate precipitous and sustained increase from baseline in viral load of greater than 0.5 logs, then the viral load will then be followed every other day for 7 days to determine if the increase is a sustained result.

- If a patient-subject experiences a immediate precipitous decrease from baseline in CD4+ T-cell count of 50% or greater. CD4+ T-cell count will then be followed every other day for 7 days to determine if the decrease is a sustained result.

- If a patient-subject experiences detection of VSV-G RNA, VSV-G antibody response will be followed every other day for 7 days to determine if the detection is a sustained result.

5.3.11 Screen Failures

Patient-subjects will be considered to be a screen failure if any of the following occur:

– Patient-subject consented and is determined to be not eligible based upon results of screening procedures.

– Patient-subject consented and determined eligible for the study but develops an exclusionary condition or withdraws consent prior to dosing.

5.4 Schedule of Procedures

The evaluation schedule for the study is provided in Appendix C.

5.4.1 Screening

An investigator must explain the nature of the study protocol and risks associated with the protocol in detail to the patient-subject. The patient-subject must sign and date his/her written informed consent prior to participation in the study. The date of the Informed Consent will be recorded in the patient-subject's medical record and on the case report form. Screening procedures will include:

- A review of Inclusion/Exclusion Criteria
- Medical History
- Physical Examination including vital signs, height and weight
- Review of concomitant medications
- Hematology (WBC with differential, RBC, Hct, Hgb and platelets)
- PT and PTT
- Chemistry (Sodium, Potassium, Chloride, Bicarbonate, CO2, Urea Nitrogen, Creatinine, Glucose, Total Protein, Albumin, Calcium, Phosphorous, Alkaline Phosphatase. Total Bilirubin, Cholesterol, Triglyceride, lipase, amylase, ALT, AST, GGT, GGT, LDH)
- Urinalysis
- CD4 level (if patient-subject has a documented CD4 level within 30 days of screening this will be accepted)
- Viral Load (if patient-subject has a documented viral load within 30 days of screening this will be accepted) and Differential Viral Load (to establish comparability between standard and TaqMan RT-PCR viral load assays
- 12 lead Electrocardiogram (ECG)
- Chest X-ray (within 30 days prior to dosing)
- Serum β HCG pregnancy (women of childbearing potential).

5.4.2 Apheresis

After all required evaluations are completed and eligibility is confirmed by the principal investigator consented patient-subjects will undergo apheresis.

Patient-subjects will also have an apheresis procedure performed at the six-month follow up timepoint.

5.4.3 Prior to Dosing

Within twenty-four (24) hours prior to patient-subject receiving Autologous CD4 T Cells Transduced with VRX496 the following must be performed:

- Physical Exam (including vital signs)
- Chemistry
- Hematology
- PT and PTT
- Urinalysis
- Serum Pregnancy Test (for women of childbearing potential)
- 12- lead ECG
- CD4+ T-cell counts
- Differential Viral Load
- Anti-HIV immune response – ELISPOT
- Anti-HIV & Anti-Tetanus Toxoid CD4 proliferation assay
- # of VRX496 modified Cells
- VSV-G RNA in plasma
- VSV-G antibody response
- Review of Concomitant Medications
- Adverse Events

5.4.4 VRX496 Administration

- On the day of patient-subject dosing, VRX496-modified T cells will be transported from the Clinical Cell Production Facility to the study site at University of Pennsylvania Hospital.
- VRX496-modified T cells will be thawed in a 37°C water bath at patient-subject bedside immediately after transport. Cells will be infused within 5-30 minutes after thaw.
- The VRX496-modified T cells (approximately 1.0×10^8 cells/mL) drug product will be immediately infused intravenously at a rate of

approximately 10 mL/minute through a 18G latex free Y-type blood set with 3 way stop-cock. Dosing will take place by gravity infusion. If the infusion rate by gravity is too slow, the VRX496-modified T cells drug product may be drawn into a 50mL syringe via the stopcock and manually infused at the required rate. The infusion volumes for each dose level are as follows:

Dose Level 1 (approximately $1.0x10^9$ cells) – approximately 10 mL

Dose Level 2 (approximately $3.0x10^9$ cells) – approximately 30 mL

Dose Level 3 (approximately $1.0x10^{10}$cells) – approximately 100 mL

Dose Level 4 (approximately $3.0x10^{10}$ cells) – approximately 300 mL

- Within 15 minutes (± 5 minutes) following completion of dosing with VRX496 modified T-cells a blood sample will be obtained for VRX496containing T-lymphocytes.
- Blood pressure, heart rate, respiratory rate and pulse oximetry will be obtained and recorded immediately prior to dosing and every 15 minutes for 2 hours following the start of infusion. If vital signs are not stable 2 hours following the start of infusion, measurements will continue to be obtained every 15 minutes until the patient-subject's vital signs are stable
- Patient-subjects will remain in the inpatient Clinical Research Center (CRC) for 2 hours post infusion for observation. If no symptoms occur and patient-subject's vital signs are stable, patient-subject will be discharged.
- Patient-subjects will be instructed to return to the CRC in 24 hours for blood tests and follow up.

5.4.5 Twenty-Four (24) hours after Dosing

- Physical Exam (including vital signs)
- Chemistry
- Hematology
- PT and PTT
- Urinalysis
- 12 lead ECG

- Review of Concomitant Medications
- Adverse Events

5.4.6 Forty-eight (48) hours after Dosing

- Physical Exam (including vital signs)
- Review of Concomitant Medications
- Adverse Events

5.4.7 Seventy-two (72) hours after Dosing

- Physical Exam (including vital signs)
- Chemistry
- Hematology
- Urinalysis
- CD4+ T-cell counts
- Differential Viral Load
- Anti-HIV immune response – ELISPOT
- Anti-HIV & Anti-Tetanus Toxoid CD4 proliferation assay
- # of VRX496 modified Cells
- VSV-G RNA in plasma
- VSV-G antibody response
- Review of Concomitant Medications
- Adverse Events

5.4.8 Seven (7) Days post dosing

- Physical Exam
- Chemistry
- Hematology
- Urinalysis
- CD4+ T-cell counts
- Differential Viral Load
- Anti-HIV immune response – ELISPOT
- Anti-HIV & Anti-Tetanus Toxoid CD4 proliferation assay
- # of VRX496 modified Cells
- VSV-G RNA in plasma

- VSV-G antibody response
- Review of Concomitant Medications
- Adverse Events

5.4.9 Fourteen (14) Days post dosing

- Physical Exam (including vital signs)
- Review of Concomitant Medications
- Adverse Events

5.4.10 Twenty-eight (28) Days post dosing

- Physical Exam (including vital signs)
- 12 lead ECG
- CD4+ T-cell counts
- Differential Viral Load
- Anti-HIV immune response – ELISPOT
- Anti-HIV & Anti-Tetanus Toxoid CD4 proliferation assay
- # of VRX496 modified Cells
- VSV-G RNA in plasma
- VSV-G antibody response
- TCR Vβ diversity analysis
- Chest X-ray
- Hematology
- PT/PTT
- Chemistry
- Urinalysis
- Review of Concomitant Medications
- Adverse Events

5.4.11 Three (3)-months post dosing

- CD4+ T-cell counts
- Differential Viral Load
- Anti-HIV immune response – ELISPOT
- Anti-HIV & Anti-Tetanus Toxoid CD4 proliferation assay
- # of VRX496 modified Cells

- VSV-G RNA in plasma
- VSV-G antibody response

5.4.12 Six (6)-months post dosing

- CD4+ T-cell counts
- Differential Viral Load
- Anti-HIV immune response – ELISPOT
- Anti-HIV & Anti-Tetanus Toxoid CD4 proliferation assay
- # of VRX496 modified Cells
- VSV-G RNA in plasma
- VSV-G antibody response
- Biological RCR test
- Second research Apheresis
- Medical History

5.4.13 One year post dosing and annually for life

- CD4+ T-cell counts
- Differential Viral Load
- Anti-HIV immune response – ELISPOT
- Anti-HIV & Anti-Tetanus Toxoid CD4 proliferation assay
- # of VRX496 modified Cells
- VSV-G RNA in plasma
- VSV-G antibody response
- Medical History

Note: If all post treatment assays are negative during the first year, the yearly samples should be archived. Samples should be archived with appropriate safeguards to ensure long-term storage (e.g., a monitored freezer alarm storage system) and an efficient system for the prompt linkage and retrieval of the stored samples with the medical records of the patient-subject and the production lot records.

If any post-treatment samples are positive, further analysis and more extensive patient-subject follow-up should be undertaken. At the time of collection of yearly patient-subject specimens, a brief clinical history should be obtained. This history should be targeted towards determination of clinical outcomes suggestive of retroviral disease.

5.5 Premature Discontinuation of Study Patient-subjects

A patient-subject is considered to be a premature discontinuation if their participation is terminated prior to completion of all required visits/evaluations specified in Sections 5.4.1 through 5.4.13 of the protocol.

A patient-subject may be discontinued for the following reasons:

- Non-Compliance with treatment regimen or follow up requirements
- Lost To Follow-Up
- Patient-subject Request for Voluntary Withdrawal
- Adverse Event
- Investigator Decision

If a patient-subject is prematurely discontinued prior to Day-28 from the study, all Day-28 procedures will be performed. If a patient-subject is prematurely discontinued following the Twenty-eight (28) Day evaluation, all 6-month procedures will be performed.

5.6 Recording of Adverse Events

Each patient-subject will be observed and queried in a nonspecific fashion by the investigator or his/her designee at each visit during the study for any new or continuing AEs since the previous visit. Any AE reported by the patient-subject or noted by the investigator or his/her designee will be recorded on the Adverse Experience Case Report Form. The following information will be recorded for each reported AE: description of the event, time of onset, time of resolution, severity, drug relationship determination, outcome, and management of the AE.

5.6.1 Potential Adverse Events

This is the first protocol using VRX496 in humans and the safety profile in humans is unknown. Adverse clinical events reported in clinical trials with infusion of gene-modified T-cells have been chills, fever, headache, nausea, rigors, bronchospasm, myalgias and blurred vision.

Patient-subjects may also experience a metallic taste in the mouth, hypertension, bradycardia, allergic reaction, and seizures due to the DMSO component of the final formulation. Nausea, vomiting, decreased hemoglobin and hematocrit, increased AST and ALT, hypersensitivity reaction anaphylaxis and thrombophlebitis may be observed from the Dextran-40 component of the formulation.

The apheresis procedure may be associated with the following adverse events: nausea, vomiting, seizures, blood loss, infection, skin rash, flushing, hives, numbness and tingling, bruising at the site of venous access, lightheadedness, and lower extremity edema.

5.6.2 Definitions

Adverse events (AEs) are defined as Treatment Emergent Signs and Symptoms (TESS). These are events that are not seen at screening, or, if present at screening have worsened in severity.

Study drug relationship for each adverse experience should be determined by the investigator using the following definitions:

NOT RELATED:
This category applies to those adverse experiences, which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).

UNLIKELY: (Must have 2)
In general, this category can be considered applicable to those adverse experiences, which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug. An adverse experience may be considered unlikely to be related if or when:

The adverse experience does not follow a reasonable temporal sequence* from administration of the study drug.

The adverse experience could readily have been produced by the patient-subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient-subject.

The adverse experience does not follow a known response pattern to the suspected drug.

It does not reappear or worsen when the drug is re-administered.

POSSIBLY: (must have 2)

This category applies to those adverse experiences for which, after careful medical consideration at the time they are evaluated, a connection with the study drug administration appears unlikely but cannot be ruled out with certainty. An adverse experience may be considered possibly related if or when:

The adverse experience follows a reasonable temporal sequence from the time of drug administration.

The adverse experience follows a known response pattern to the study drug.

The adverse experience could have been produced by other factors such as the patient-subject's clinical state, therapeutic interventions, or concomitant drugs administered to the patient-subject.

LIKELY: (must have 3)

This category applies to those adverse experiences, which, after careful medical consideration at the time they are evaluated, are felt with a high

*Temporal sequence is defined as an association between the suspect drug and the observed reaction or event in which the suspect drug was present prior to the reaction or event as defined by history or drug blood level.

degree of certainty to be related to the study drug. An adverse experience may be considered likely related if or when:

The adverse experience follows a reasonable temporal sequence from the time of drug administration.

The adverse experience follows a known response pattern to the study drug.

The adverse experience cannot be reasonably explained by other factors such as the patient-subject's clinical state, therapeutic interventions, or concomitant drugs administered to the patient-subject.

The adverse experience is confirmed by improvement of the symptoms on de-challenge (e.g., the removal withdrawal, or discontinuation of the suspected drug from the patient-subject's therapeutic regimen).

DEFINITELY: (must have all 4)

This category applies to those adverse experiences, which the Investigator feels are incontrovertibly related to the study drug. An adverse experience may be assigned an attribution of definitely related if or when:

The adverse experience follows a reasonable temporal sequence from the time of drug administration.

The adverse experience cannot be reasonably explained by the known characteristics of the patient-subject's state, environmental or toxic factors, or other modes of therapy administered to the patient-subject.

The adverse experience occurs immediately following study drug administration, or improves on stopping the drug (de-challenge), or reappears on repeat exposure (re-challenge) (Note: this is not to be construed as requiring re-exposure of the patient-subject, however, a category of definitely related can only be used when recurrence is observed).

The adverse experience follows a known response pattern to the study drug.

NOTE: The decision to perform a formal re-challenge must be made by the TheraSolutions/VIRxSYS medical monitor and the investigator after reviewing the subject's complete history.

Severity of an adverse experience is defined as a qualitative assessment of the degree of intensity of an adverse experience as determined by the investigator or reported to him/her by the patient-subject. The assessment of severity is made irrespective of drug relationship or seriousness of the event and determined using the Toxicity Criteria in Appendix A. The severity of adverse events not listed in Appendix A will be rated according to the following 3-point scale:

Mild:
Symptom barely noticeable to patient-subject; does not influence performance or functioning. Prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of patient-subject.

Moderate:
Symptom of a sufficient severity to make patient-subject uncomfortable; performance of daily activities influenced; patient-subject is able to continue in study; treatment for symptom(s) may be needed.

Severe:
Symptom causes severe discomfort; may be of such severity that patient-subject cannot continue in study and may cause cessation of treatment with study drug; treatment for symptom(s) may be given and/or patient-subject hospitalized.

All serious adverse experiences must be reported to TheraSolutions and VIRxSYS, the sponsor, immediately by telephone. The patient-subject must be monitored carefully until the condition disappears and/or the etiology is defined.

All serious adverse experiences must be reported by the investigator to their IRB in writing.

5.7 Recording of Concomitant Therapy

All prescription and nonprescription medication taken by the patient-subject from screening to Day 28 of the study will be recorded on the CRF. Any additions, deletions, or changes in the dose of these medications should be entered on this form.

6.0 STATISTICAL PROCEDURES

6.1 Determination of Sample Size

Up to 24 evaluable patient-subjects will be enrolled in the study. A sample size of 3 to 6 patient-subjects per dose group was based on the number of patient-subjects deemed necessary to provide adequate clinical evidence of safety at each dose level and to determine the maximum tolerated dose. The sample size was not derived for the intention of making statistical inferences regarding the safety, efficacy, or pharmacokinetics of VRX496-modified T-cells.

6.2 Predetermined Reasons for Exclusion from Analysis

All patient-subjects receiving VRX496-modified T-cells will be included in the analysis for safety and efficacy.

6.3 Data Analysis

Due to the small sample size of each treatment group, no statistical comparisons will be made among treatment groups.

6.3.1 Safety

Laboratory safety parameters at each evaluation period will be presented for each study patient-subject. Differences in changes from baseline among dose levels will be evaluated through group summary statistics and graphical presentations of individual patient-subject profiles.

Adverse events will be listed for each study patient-subject. Proportion of patient-subjects experiencing adverse events at each dose level will be

presented for each evaluation period by adverse event term and body system, as well as severity and relationship to VRX496.

12-lead electrocardiogram and chest x-ray findings will be compared to baseline and presented as either normal or abnormal for each patient-subject and evaluation period. The proportion of patient-subjects with negative changes from baseline (i.e., normal to abnormal) will be presented by dose level and evaluation period. Specific abnormalities that occur during the course of the study will be recorded as adverse events.

6.3.2 Secondary Evaluations

Secondary evaluation parameters (CD4+ T-cell counts, differential viral load, VSV-G antibody responses, TCR Vβ diversity analysis, anti-HIV and anti-Tetanus Toxoid immune response as measured by CD4 proliferation assay , and anti-HIV CD8 immune response as measured by ELISPOT) at each evaluation period will be presented for each study patient-subject. Differences in changes from baseline among dose levels will be evaluated through group summary statistics (e.g., means) and graphical presentations of individual patient-subject profiles.

6.3.3 Cell Survival

Concentrations of VRX496 containing T-lymphocytes will be presented for each study patient-subject. Differences in changes from baseline among dose levels will be evaluated through group summary statistics and graphical presentations of individual patient-subject profiles.

6.4 Interim Analysis

No interim analysis is planned for this study.

7.0 CLINICAL TEST ARTICLES

7.1 Description

The test article used in this study is the patient-subject's autologous T-cells transduced with VRX496, referred to as the VRX496 drug product. The VRX496 drug product will be packaged in cryocyte bags containing VRX496 transduced T-cells (at a concentration of approximately 1.0 $x10^8$ cells/mL) in an aliquot (volume dependent upon dose) of cryomedia containing 31.25% Plasmalyte-A, 31.25% Dextrose (5%), 0.45% NaCl, 7.5% DMSO, 1% Dextran 40 and 5% human serum albumin. VRX496 is prepared under an IND that will be maintained by VIRxSYS Corporation. The autologous T cells will be transduced with VRX496 under a physician-sponsored IND maintained by C. H. June, M.D. at the University of Pennsylvania.

7.2 Packaging and Labeling

The VRX496 drug product will be packaged in a cryocyte 250 mL bag that is labeled with a 2-part perforated label containing unique patient-subject and product identifiers. The product will be frozen at less than –130°C in an electric freezer with LN_2 back-up that minimizes the potential for cross contamination of patient-subject cells. A sample label is provided in Appendix C.

7.3 Storage Conditions

VRX496 drug product will be cryopreserved at the Clinical Cell and Vaccine Production Facility (CVPF) at University of Pennsylvania. Containers of VRX496 are stored at the CVPF in a dedicated and monitored freezer.

On the day of patient-subject dosing, VRX496 drug product will be transported from the Clinical Cell Production Facility to the Clinical Research Center (CRC) at University of Pennsylvania Hospital packaged on dry ice. The cells will be thawed at the patient-subject's bedside and infused on the same day as shipment. Cells should be infused within 5-30 minutes after thaw.

7.4 Accountability

The investigator must maintain an accurate record of all drug received. Medications dispensed for all patient-subjects must be recorded on the Drug

Accountability Form. This form must be available at all times for inspection by the TheraSolutions monitor. The dispensing log must include:

- Patient-subject Number and Initials
- Patient-subject's Date of Birth
- Date Drug Dispensed
- Amount Used
- Amount Wasted (if applicable)
- Amount Remaining In Stock

The dispensing log will be reviewed at each monitoring visit.

The study medication supplied for this study is only for use in patient-subjects properly consented and enrolled under this protocol. These drugs must be kept physically separate from standard clinic or office drug supplies.

8.0 ADMINISTRATIVE

8.1 Serious Adverse Experience Reporting

A serious adverse experience is defined as any event that results in one of the following outcomes:

- death (i.e., fatal);
- life-threatening;
- results in a persistent or significant disability/incapacity;
- requires or prolongs inpatient hospitalization;
- a congenital anomaly, or birth defect; or
- based upon appropriate medical judgment, the experience may jeopardize the patient-subject and may require medical or surgical intervention to prevent one of the aforementioned outcomes.

Any serious adverse experience will be reported immediately to the TheraSolutions and VIRxSYS contacts listed below:

Catherine Van Doren, RN
TheraSolutions
620 Professional Drive
Gaithersburg, MD 20879
(240) 631-6153
(877) 670-8437, ext 153

and

Boro Dropulic, PhD
VIRxSYS Corporation
200 Perry Parkway, Suite 1A
Gaithersburg, Maryland 20877
(301) 987-0480, EXT 223
CELL (443) 310 7724

Reporting will be in the form of the following:

- the serious adverse experience form; and
- any additional documentation (i.e., autopsy report, hospital records, ECG's, laboratory tests) required to support or adds to information in the serious adverse experience form.

In addition, the Principal Investigator will immediately report all Serious Adverse events to their local IRB in accordance with the Institutions Standard Operating Procedures.

Follow-up to the initial reporting of the experience the following documentation must be forwarded to VIRxSYS Corporation, and its clinical trial management contractor, TheraSolutions.

All serious adverse experiences that are reported to US regulatory authorities as a 7 or 15-day report must also be submitted to the IRB in writing.

8.1.1 Non-Serious Adverse Experience Reporting

Non-serious adverse experiences will be reported on the appropriate case report form (CRF) as described in Section 5.6. The sponsor is responsible for the reporting of non-serious adverse experiences to the FDA in the IND annual report.

8.2 Case Report Forms

All case report forms (CRFs) are to be completed within one month of patient-subject evaluation. A CRF is provided for each patient-subject. All forms must be completed in black ink or typed. The CRFs are not to be used as the

primary method for collecting study data. CRFs are intended for the transcription data collected for the study from source documents.

All entries on the CRF must be supported by original source documentation (i.e., laboratory reports) maintained at the investigational site.

Correction(s) of data on the CRF can only be made by crossing out the incorrect data (in a manner that leaves the previous entry identifiable) and writing the correct values next to those crossed out. Each correction must be initialed and dated by the individual making the correction.

The investigator is required to review all entries on the CRF and sign where indicated to attest to the accuracy of the data recorded on the form.

8.3 Investigator Requirements

8.3.1 Prior to Study Initiation

Prior to study initiation, the investigator will forward the following essential documentation to TheraSolutions.

A signed and dated FDA 1572 Statement of Investigator form plus current curriculum vitae for each individual named on the form.

A signed and dated investigator agreement (page 40 of the protocol).

Identification of the clinical laboratory facilities that will be used including certification (i.e., CLIA, CAP or State Licenses) or proficiency ratings, and normal ranges for the determinations described by the protocol, and a copy of the curriculum vitae for the lab director.

A copy of the formal written notification of approval of the protocol and consent form, to the investigator from the IRB, in compliance with FDA regulations (The written notification of "Action" is to be signed by the chairman or any persons authorized in the IRB's SOPs).

A list of institutional review board members and their respective titles, occupations, and institutional affiliations or provide a general assurances number for the IRB.

An actual copy of the IRB-approved informed consent form and other adjunctive materials to be used in this study to elicit and record patient-subject consent in compliance with Food and Drug Administration (FDA) regulations.

Documentation to assure local regulations (e.g., California, Oregon and Massachusetts state regulations) have been met, if applicable.

8.3.2 Informed Consent

The informed consent should be given by means of a standard written statement. It should be written so as to be easily understood by the patient-subject. The patient-subject should be given the time to read and understand the statement and be afforded the opportunity to ask questions before signing his/her consent and dating the document. The patient-subject should receive a copy of the written statement once he/she and the Investigator have signed the informed consent.

VIRxSYS, with its clinical trial management contractor TheraSolutions, will review the proposed informed consent form for content prior to submission to the IRB/Ethical Committee. The informed consent form must be considered as a part of the protocol with which it is to be submitted by the Investigator for approval to the IRB/Ethics Committee.

The informed consent form must contain the following elements:

- That the trial involves research.
- The purpose of the trial.
- The trial treatment(s) and the probability for random assignment to each treatment.
- The trial procedures to be followed, including all invasive procedures.
- The patient-subject's responsibilities.
- Those aspects of the trial that are experimental.

- The reasonably foreseeable risks or inconveniences to the patient-subject and, when applicable, to an embryo, fetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the patient-subject, the patient-subject should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the patient-subject, and their important potential benefits and risks.
- The compensation and/or treatment available to the patient-subject in the event of trial-related injury.
- The anticipated prorated payment, if any, to the patient-subject for participating in the trial.
- The anticipated expenses, if any, to the patient-subject for participating in the trial.
- That the patient-subject's participation in the trial is voluntary and that the patient-subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the patient-subject is otherwise entitled.
- That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the patient-subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the patient-subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the patient-subject or the patient-subject's legally acceptable representative is authorizing such access.
- That records identifying the patient-subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the patient-subject's identity will remain confidential.
- That the patient-subject or the patient-subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the patient-subject's willingness to continue participation in the trial.
- The person(s) to contact for further information regarding the trial and the rights of trial Patient-subjects, and whom to contact in the event of trial-related injury.
- The foreseeable circumstances and/or reasons under which the patient-subject's participation in the trial may be terminated.
- The expected duration of the patient-subject's participation in the trial.
- The approximate number of Patient-subjects involved in the trial.

8.3.3 Institutional Review Boards

The investigator assures that the Institutional Review Board (IRB) responsible for the initial and continuing review and approval of this clinical study complies with the requirements set forth in 21 CFR Part 56.

The investigator also assures that he/she will promptly report to the IRB all changes in research activity and all unanticipated problems involving risks to human patient-subjects or others, and that he/she will not make any changes in the research until the IRB has approved the changes and VIRxSYS has notified the FDA, except where necessary to eliminate immediate hazards to human patient-subjects. Documentation of approval or notification must be forwarded directly to VIRxSYS, and its clinical contractor TheraSolutions, for any amendment.

The investigator must also report to his/her IRB at least yearly on the progress of the investigation and obtain written approval to continue the study beyond the time stated in the original approval. The investigator must notify the IRB of the conclusion of the study within three months after completion, termination or discontinuation of the study. Documentation of the annual progress report to the IRB, renewal of IRB approval, and notification of study conclusion must be provided directly to VIRxSYS and its clinical contractor, TheraSolutions.

8.3.4 Records Retention

US Federal law requires that a copy of all records (e.g., informed consent documents, laboratory data slips, source documents, IND safety reports, test article dispensing records, etc.) which support case report forms of this study, must be retained in the files of the responsible investigator for a minimum of two years following notification by VIRxSYS that:

- all investigations at all sites are completed, terminated, or discontinued; or
- the last marketing application in an ICH region (including US Food and Drug Administration) has been approved; and
- there are no pending or contemplated marketing applications in an ICH region.

VIRxSYS may use data generated by this protocol to support regulatory filings in other countries. In order to be in compliance with foreign regulatory agencies, the investigator is required to maintain all study records for a period of 10 years following the conclusion of this study.

If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. VIRxSYS, and its clinical contractor TheraSolutions, must be notified in writing of the name and address of the new custodian.

8.3.5 Accountability and Storage of Materials

Test Articles - The investigator is responsible for maintaining an accurate, up-to-date dispensing log for all study drugs supplied by VIRxSYS that includes the following: Patient-subject number, date study drug dispensed, quantity dispensed, quantity returned, and amount wasted. All study medication received and dispensed by the investigator will be inventoried and accounted for throughout the study. The study medication must be stored in a restricted area with limited access. Contents of the study medication containers must not be combined.

Patient Samples – Retention of patient samples is the responsibility of the principal investigator and the laboratory that performs the tests. Retention samples will be archived throughout the duration of the study and for the period as required by the FDA.

8.4 On-site Monitoring and Audits

A representative of VIRxSYS (or its clinical trial management contractor, TheraSolutions) will periodically monitor the study beginning with patient-subject enrollment and at intervals not exceeding two months. The monitor will assess protocol compliance, maintenance of proper documentation of study procedures (including informed consent), proper reporting of adverse events, accuracy of data recoded on case report forms, and test article accountability.

It is the responsibility of the Principal Investigator to provide all study records, including case report forms, source documents, etc., for review and inspection by the monitor at their visit. The Principal Investigator is also responsible to be available to meet with the monitor to discuss visit findings at the conclusion of each visit.

The US Food and Drug Administration and other foreign regulatory authorities, in the person of a scientifically trained and properly authorized employee of the agency, may request access to all study records, including source documents, for inspection and copying.

8.5 Amendments to the Protocol

Neither the investigator nor VIRxSYS will amend or modify the protocol without notification of the other. All amendments must be approved by VIRxSYS prior to implementation. All amendments must be submitted to the IRB for their notification/approval.

8.6 Departure from Protocol

Departure from study protocol is generally not permitted. Should an occasion occur in which the protocol has not been followed, the investigator is required to provide directly to VIRxSYS, and its clinical trial management contractor, with a written description of the reason(s) that the protocol was not followed and what remedial action will be taken to prevent future occurrences.

Repeated departures from the protocol will result in the immediate removal of the investigator and/or termination of the investigational site.

8.7 Duration of Trial and Circumstances for Termination

The investigator agrees to complete his portion of this study within 9 months after study initiation. Extension beyond this timeframe is at the discretion of VIRxSYS Corporation. It is agreed that, for reasonable cause, either the investigator or the sponsor, VIRxSYS, may terminate this study, provided written notice is submitted at a reasonable time in advance of intended

termination. VIRxSYS reserves the right to terminate the study without advance notice under the following circumstances:

- noncompliance with the protocol;
- slow enrollment (i.e., insufficient to reasonably complete the study within the prescribed timeframe);
- discontinuation of the study protocol;
- discontinuation of all studies of the test drug; and
- withdrawal of the IND.

8.8 Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) comprised of three physicians with experience in HIV infection and/or gene transfer therapy will be assembled and will work under a charter specifically developed for safety oversight of this study. The DSMB will meet to evaluate patient-subject safety at the following study milestones:

- After the initial patient-subject completes 28 day follow up
- After completion of Dose level 1
- After completion of Dose level 2
- After completion of Dose level 3

If necessary, additional meeting of the DSMB may be held if safety issues arise in between scheduled meetings.

8.9 Financial Disclosure

The clinical investigator participating in this study is required to provide sufficient and accurate financial information for the clinical investigator, their spouse and dependent children to the sponsor pertaining to:

- Any arrangement between the sponsor and clinical investigator whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- Any significant payments of other sorts from the sponsor, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

- Any proprietary interest in the tested product held by the investigator involved in any study.
- Any significant equity interest in the sponsor held by any clinical investigator involved in the study.

The investigator will provide this information to the sponsor at the beginning of the investigators participation in the study and agree to provide the sponsor with prompt updates of any relevant changes in financial information for the course of the study and for one year following completion of the study.

9.0 REFERENCES

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10.0 INVESTIGATOR AGREEMENT

I have read the VIRxSYS protocol, A Phase 1 Open-Label Clinical Trial of The Safety and Tolerability of Single Escalating Doses of VRX496 in HIV Positive Patient-subjects and agree that it contains all necessary details for performing this study. I will conduct this in compliance with the study protocol, current Good Clinical Practice (cGCP) guidelines, and all applicable regulatory requirements, and will complete the study within the time designated. I will complete all required documentation related to regulatory requirements.

I will provide copies of the protocol and all information on the study drug relating to pre-clinical and prior clinical experience which as furnished to me by the sponsor to all physicians, nurses and other personnel responsible to me who participate in this study and will discuss this material with them to assure that they are fully informed regarding the study drug and the conduct of the study.

I agree that the conduct and results of this study will be kept confidential. I agree that the case report forms and other data pertinent to this study are property of VIRxSYS who may utilize the data in various ways, such as for submission to government regulatory authorities, or in publication of the results of multi-center study, if applicable. I further agree that VIRxSYS, or its clinical contractor , shall have access to any source documents from which case report form information may have been generated.

I will submit this protocol to my IRB for approval.

_____ _____

Name
Title

Date

Appendix A

Toxicity Criteria

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE THREATENING
HEMATOLOGY				
Hemoglobin	8.0 g/dL - 9.4 g/dL	7.0 g/dL - 7.9 g/dL	6.5 g/dL - 6.9 g/dL	<6.5 g/dL
Absolute Neutrophil Count	1000 - 1500/mm^3	750 - 999/mm^3	500 - 749/mm^3	<500/mm^3
Platelets	75,000 - 99,000/mm^3	50,000 - 74,999/mm^3	20,000 - 49,999/mm^3	<20,000/mm^3
Prothrombin Time (PT)	>1.0 - 1.25 X ULN	>1.25 - 1.5 X ULN	>1.5 - 3.0 X ULN	>3 X ULN
PTT	>1.0 - 1.66 x ULN	>1.66 - 2.33 x ULN	>2.33 - 3.0 x ULN	>3.0 x ULN
Methemoglobin	5.0 - 10.0%	10.1 - 15.0%	15.1 - 20.0%	>20%
CHEMISTRIES				
SODIUM				
Hyponatremia	130 - 135 meq/L	123 - 129 meq/L	116 - 122 meq/L	<116 meq/L
Hypernatremia	146 - 150 meq/L	151 - 157 meq/L	158 - 165 meq/L	>165 meq/L
POTASSIUM				
Hypokalemia	3.0 - 3.4 meq/L	2.5 - 2.9 meq/L	2.0 - 2.4 meq/L	<2.0 meq/L
Hyperkalemia	5.6 - 6.0 meq/L	6.1 - 6.5 meq/L	6.6 - 7.0 meq/L	>7.0 meq/L
PHOSPHATE				
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 - 1.9 mg/dL	1.0 - 1.4 mg/dL	<1.0 mg/dL
CALCIUM - (corrected for albumin)				
Hypocalcemia	7.8 - 8.4 mg/dL	7.0 - 7.7 mg/dL	6.1 - 6.9 mg/dL	<6.1 mg/dL
Hypercalcemia	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	>13.5 mg/dL
MAGNESIUM				
Hypomagnesemia	1.2 - 1.4 meq/L	0.9 - 1.1 meq/L	0.6 - 0.8 meq/L	<0.6 meq/L
BILIRUBIN				
Hyperbilirubinemia	>1.0 - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 - 5 x ULN	>5 x ULN

GLUCOSE				
Hypoglycemia	55 - 64 mg/dL	40 - 54 mg/dL	30 - 39 mg/dL	<30 mg/dL
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161 - 250 mg/dL	251 - 500 mg/dL	>500 mg/dL
Triglycerides		400 - 750 mg/dL	751 - 1200 mg/dL	>1200 mg/dL
Creatinine	>1.0 - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
URIC ACID				
Hyperuricemia	7.5 - 10.0 mg/dL	10.1 - 12.0 mg/dL	12.1 - 15.0 mg/dL	>15.0 mg/dL
LIVER TRANSAMINASE (LFTs)				
AST (SGOT)	1.25 - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10.0 x ULN	>10.0 x ULN
ALT (SGPT)	1.25 - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10.0 x ULN	>10.0 x ULN
GGT	1.25 - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10.0 x ULN	>10.0 x ULN
Alk Phos	1.25 - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10.0 x ULN	>10.0 x ULN
PANCREATIC ENZYMES				
Amylase	>1.0 - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
Pancreatic amylase	>1.0 - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
Lipase	>1.0 - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
CARDIOVASCULAR				
Cardiac Arrhythmia		Asymptomatic; transient dysrhythmia,no Rx req	Recurrent/persistent dysrhythmia; symptomatic Rx req	Unstable dysrhythmia, hospitalization and Rx req
Hypotension	Transient orthostatic hypotension, no Rx	Sx correctable with oral fluid Rx	IV fluid req, no Hospitalization req	hospitalization req
Hypertension	Transient, increase >20 mm/Hg; no Rx	Recurrent; chronic increase >20 mm/Hg	Acute Rx req; outpatient hospitalization possible	Hospitalization req
Pericarditis	Minimal effusion	Mild/mod asymptomatic effusion, no Rx	Symptomatic effusion, pain, EKG changes	Tamponade OR pericardiocentesis OR surgery req
Hemorrhage, blood Loss		Mildly symptomatic no	Gross blood loss OR 1-2	Massive blood loss OR >2

GASTROINTESTINAL				
Nausea	Mild OR transient; reasonable intake maintained	Mod discomfort OR intake decreased for <3 days	Severe discomfort OR minimal intake for ≥3 days	Hospitalization req
Vomiting	Mild OR transient;2-3 episodes per day OR mild vomiting lasting <1 week	Mod OR persistent; 4-5 episodes per day; OR vomiting lasting ≥1 week	Severe vomiting of all food/fluids in 24 hrs OR orthostatic hypotension IV Rx req	Hypotensive shock OR hospitalization req for IV Rx req
Diarrhea	Mild OR transient;3-4 loose stools perday OR mild diarrhea lasting <1 week	Mod OR persistent;5-7 loose stools perday OR diarrhealasting ≥1 week	Bloody diarrhea; OR orthostatic hypotension OR >7 loose stools/day OR IV Rx required	Hypotensive shock OR hospitalization req
Oral Discomfort/Dysphagia	Mild discomfort, no difficulty swallowing	Difficulty swallowing but able to eat and drink	Unable to swallow solids	Unable to drink fluids; IV fluids req
Constipation	Mild	Moderate	Severe	Distention with vomiting
RESPIRATORY				
Cough (foraerosol studies)	Transient; no Rx	Treatment associated cough; inhaled bronchodilator	Uncontrolled cough;systemic Rx req	
Bronchospasm Acute	Transient; no Rx; FEV1 70% - <80%(or peak flow)	Rx req; normalizes with bronchodilator; FEV1 50% - <70% (or peak flow)	No normalization with bronchodilator; FEV1 <25% - 50%(or peak flow) . retractions	Cyanosis; FEV1 25% (or peak flow) or intubated
Dyspnea	Dyspnea onexertion	Dyspnea with normal activity	Dyspnea at rest	Dyspnea requiring O_2 therapy

NEUROLOGIC				
Neuro-cerebellar	Slight incoordinationOR dysdiadochokinesia	Intention tremor OR dysmetria OR slurredspeech OR nystagmus	Ataxia requiring assistance to walk or arm incoordination interfering with ADLs	Unable to stand
Neuro-psych/mood	———	———	Severe mood changesrequiring medical intervention	Acute psychosis req hospitalization
Paresthesia	Mild discomfort; no Rx req	Mod discomfort; non-narcotic analgesia req	Severe discomfort; OR narcotic analgesia req with symptomatic improvement	Incapacitating; OR not responsive narcotic analgesia
Neuro-motor	Mild weakness in muscle of feet but able to walk and /or mild increase or decrease in reflexes	Mod weakness in feet (unable to walk on heels and/or toes), mild weakness in hands, still able to do most tasks and/or loss of previously present reflex or development of hyperrflexia and/or unable to deep deep knee bends due to weakness	Marked distal weakness (unable to dorsiflex toes or foot drop), and proximal weakness e.g., in hands,with ADLs and/or requiringassistance to walk and/or unable to rise from chair unassisted	Confined to bed orwheel chair because ofmuscle weakness
Neuro-sensory	Mild impairment (decsensation, e.g.,vibratory, pinprick,hot/cold in great toes)in focal area or symmetrical distri-bution	Mod impairment (mod dec sensation, e.g.,vibratory, pinprick,hot/cold to anklesand/or joint positionor mild impairment that is not symmetrical	Severe impairment(dec or loss of .	Sensory loss involves limbs and trunksensation to knees or) wrists) or loss of sensation of at least mod degree in multipledifferent body areas (i.e., upper and lower extremities)

URINALYSIS				
Proteinuria				
Spot urine	1+	2 -3+	4+	Nephrotic syndrome
24 hour urine	200 mg-1 g loss/day OR<0.3% OR<3 g/l	>1 - 2 g loss/day OR 0.3 - 1.0% OR 3 - 10 g/l	>2 - 3.5 g loss/day OR >1.0% OR>10 g/l	Nephrotic syndrome OR >3.5 g loss/day
Gross Hematuria	Microscopic only	Gross, no clots	Gross plus clots	Obstructive OR transfusion req
MISCELLANEOUS				
Fever	37.7 - 38.5C OR 100.0 - 101.5F	38.6 - 39.5C OR101.6 - 102.9F	39.6 - 40.5C OR103 - 105F	>40.5C OR >105F
oral >12 hours				
Headache	Mild; no Rx req	Mod; or non-narcoticanalgesia Rx	Severe; OR responds initial narcotic Rx	Intractable; OR requiring repeated narcotic Rx
Allergic Reaction	Pruritus without rash	Localized urticaria	Generalized urticaria angioedema	Anaphylaxis
Cutaneous/Rash/Dermatitis	Erythema, pruritus	Diffuse maculopapular rash OR dry desquamation	Vesiculation OR moist desquamation OR ulceration	ANY ONE: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, necrosis req surgery, exfoliative dermatitis
Local Reaction (2° parenteral Rx -not vaccination or skin test)	Erythema	Induration <10mm OR inflammation OR phlebitis	Induration >10mm OR ulceration	Necrosis of skin
Fatigue	Normal activity reduced <25%	Normal activity reduced 25-50%	Normal activity reduced >50%; cannot work	Unable to care for self

Appendix B

Schedule of Study Procedures

APPENDIX B

Schedule of Study Procedures

	Screen	Apheresis	Pre-Dosing	VRX496 Dosing	24 hrs after dosing	48 hrs after dosing	72 hours after dosing	Day 7 after dosing	Day 14 after dosing	Day 28 after dosing	3 mo. after dosing	6 mo. & yearly after dosing[4,6]
Inclusion Exclusion	X											
Informed Consent	X											
Medical History	X										X	X
Physical Examination[1]	X		X		X	X	X	X	X	X		
ECG	X		X		X					X		
Chest X-ray[2]	X									X		
CD4+ T-cell counts	X		X				X	X		X	X	X
Viral Load	X											
Diff. Viral Load	X		X				X	X		X	X	X
# VRX496 T cells			X		X		X	X		X	X	X
Anti-HIV & anti-TT CD4 proliferation	X		X				X	X		X	X	X
Anti-HIV ELISPOT	X		X				X	X		X	X	X
TCR Vβ[3]			X							X		
RT-PCR for VSV-G RNA sequence			X				X	X		X	X	X
VSV-G Ab Immunoassay			X					X		X	X	X
Biological RCR test[4]												X
Chemistry	X		X[5]		X		X	X	X	X		
Hematology	X		X[5]		X		X	X	X	X		
PT and PTT	X		X[5]		X					X		
Urinalysis	X		X[5]		X		X	X	X	X		
Serum Pregnancy Test (if applicable)	X		X[5]									
Apheresis[6]		X										X[6]
Monitor for Adverse Events				X	X	X	X	X	X	X		
Record Concomitant Medications[7]	X	X	X	X	X	X	X	X	X	X		

1 *Physical exam includes vital signs. Height will be recorded at screening. Weight will be measured at pre dosing and 28 days after dosing.*

2 *Chest X-ray will be performed within 30 days prior to dosing.*

3 *TCR Vβ diversity analysis will be performed on the first apheresed product, the VRX496 modified T cell infused product and at 28 days post dosing.*

4 *Biological RCR test will be performed only at the 6 month apheresis or once earlier if sustained VSV-G RNA is detected in the plasma.*

5 *Within 24 hours prior to administration of VRX496.*

6 *Apheresis may be done at screening (designated as the pre-study apheresis) but may require a separate visit due to scheduling. The first apheresis will be performed for gene transfer of VRX496. The second apheresis will be performed at 6 months only, unless there is sustained detection of VSV-G RNA in the patient-subject's plasma, at which time the second apheresis will be performed and biological RCR testing initiated.*

7 *Concomitant medications should be recorded 30 days prior to screening and up to and including 28 days post treatment.*

Appendix C

Sample Label for VRX496 Transduced Cells

HUMAN CD3/CD28 T-CELLS - GENE MODIFIED AUTOLOGOUS - CRYOPRESERVED

Contains _____ x 10---- Cells in _____ mL of _____

_____

Method(s) of Manipulation: _____

_____

_____

Vector: _____

Cryopreservation Date

_____

Expiration Date / Time

_____

Store at _____ °C

Recipient's Name

Recipient's Identifier

PROPERLY IDENTIFY INTENDED RECIPIENT AND COMPONENT

FOR AUTOLOGOUS USE ONLY

DO NOT IRRADIATE

WARNING: This product may transmit infectious agents.
New Drug - Limited by Federal Law to Investigational Use Only.

This product derived from Unit#_____ (*original identifier*)
collected on _____ at _____

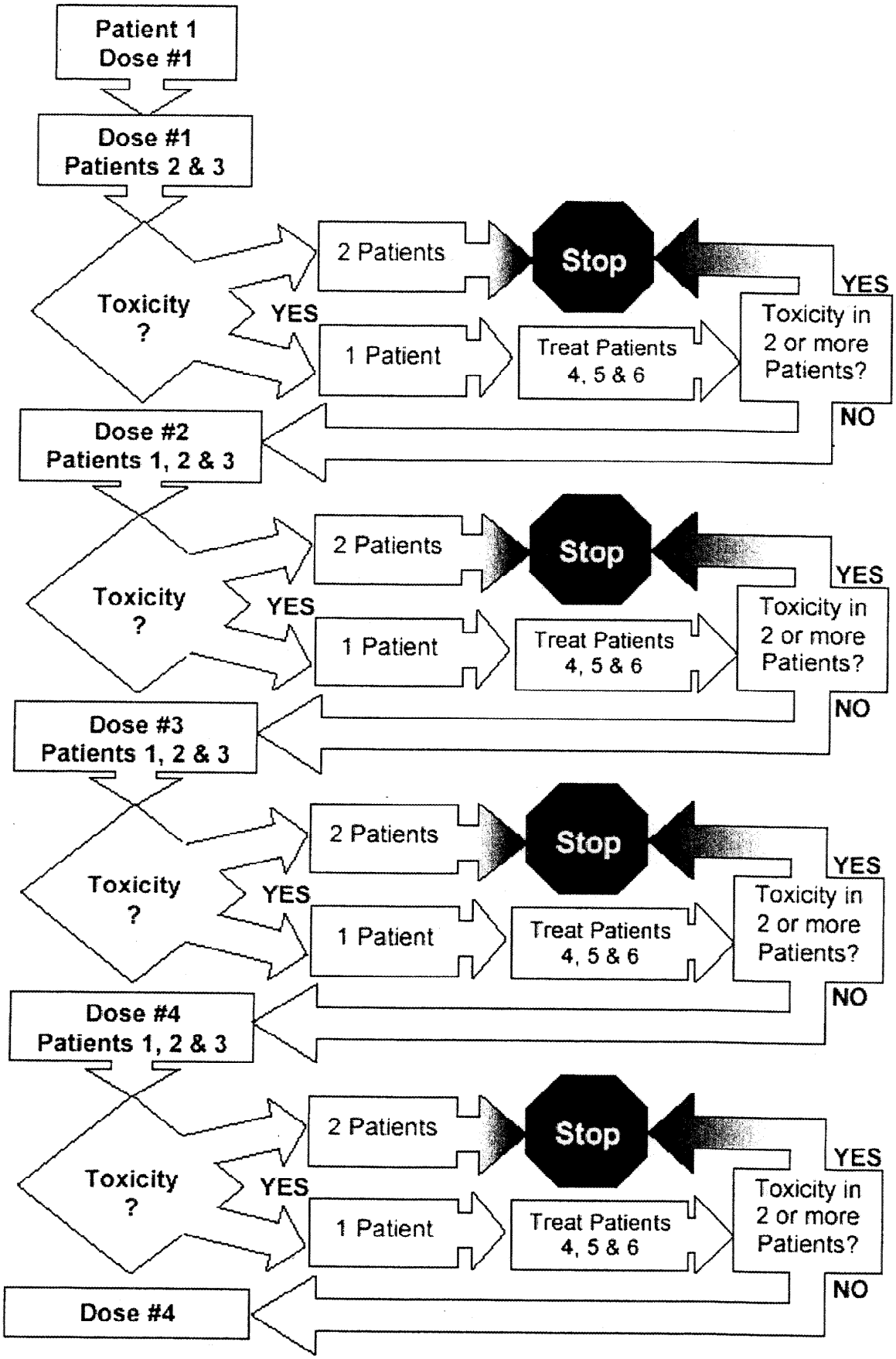
Processed by: Clinical Cell and Vaccine Production Facility Univ. of Pennsylvania Cancer Center 577 BRB 2/3, 421 Curie Blvd. Philadelphia, PA 19104-6160	*Attach Biohazard Label if required. Indicate hazard.*

CVPF Form 903-01-C

Appendix D

Dose Escalation of VRX496 Modified T Cells

Dose Escalation of VRX496 Modified T Cells



Appendix E

KARNOFSKY PERFORMANCE SCALE

KARNOFSKY PERFORMANCE SCALE

DESCRIPTION	PERCENT (%)
Normal; no complaints; no evidence of disease	100
Able to carry on normal activity; minor signs and symptoms of disease	90
Normal activity with effort; some signs and symptoms of disease	80
Cares for self; unable to carry on normal activity or do work	70
Requires occasional assistance, but is able to care for most personal needs	60
Requires considerable assistance and frequent medical care	50
Disabled; requires special care and assistance	40
Severely disabled; hospitalization indicated although death not imminent	30
Very sick; hospitalization necessary; requires active support treatment	20
Moribund; fatal processes progressing rapidly	10
Dead	0